PHYSICAL ACTIVITY, PHYSICAL FUNCTION AND ARTERIAL STIFFNESS OF PEOPLE UNDERGOING MAINTENANCE HAEMODIALYSIS FOR STAGE 5 CHRONIC KIDNEY DISEASE

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Abstract

This thesis addresses current issues regarding assessment of physical activity (PA) and physical function (PF) status of haemodialysis (HD) patients, specifically: What is the recommended wear time to provide a reliable accelerometer estimate of habitual PA and sedentary behaviour? Can similar outcomes from different accelerometers be used interchangeably? Do subjectively and objectively estimated PA outcomes agree closely enough to be pooled? Which PF assessments are potentially most 'useful'? This thesis also explores potential risk factors of arterial stiffness, a strong predictor of mortality in this population.

A PA reliability study involving 70 maintenance HD patients (55.9 ± 15.7 years) over a seven-day monitoring period indicated one dialysis day and two non-diaysis days with a minimum of eight hours wear per day would provide reliable estimates of PA and sedentary behaviour regardless of accelerometer employed, and allowed 90% sample retention. Concordance studies indicated broad agreement for similar outcomes obtained via ActivPAL and Actigraph GT3X accelerometers but they were not interchangeable. ActivPAL is recommended for monitoring steps taken and time seated, Actigraph activity count output for total/overall PA. Questionnaire and accelerometer estimated PA outcomes may not be used interchangeably or pooled. More of the shared variance of physical performance was explained by clinical, demographic and habitual PA factors than for self-reported functional status thus recommending the former. Age, blood pressure and HD vintage were determinants of arterial stiffness, however PA and cardiorespiratory fitness did not appear to be risk factors in this sample.

This thesis makes clear recommendations regarding implementation of PA and PF assessment methods, and illustrates their application on sample retention, as well as characterising and potentially identifying individuals at risk of poor outcomes. Emergence of HD vintage as a risk factor for arterial stiffness underscores the need for further research into adjunctive lifestyle interventions to manage health threats in this population.

Key words: physical activity, physical function, arterial stiffness, chronic kidney disease

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For my son Felix, and in memory of Dr Andy Payne.

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ABBREVIATIONS

ACCT	Anglo Cardiff Collaboration Trial
ACE	Angiotensin Converting Enzyme
ADL	Activities of Daily Living
AGE	Advanced Glycolated End Product
ANN	Artificial Neural Network
ANOVA	Analysis of Variance
AI	Augmentation Index
AP	Augmentation Pressure
AUC	Area Under the Curve
BM	Body Mass
BMI	Body Mass Index
BP	Blood Pressure
CDC	Comprehensive Dialysis Study
CHF	Chronic Heart Failure
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary Exercise Test
CPM	Counts Per Minute
CRF	Cardiorespiratory Fitness
CT	Computerised Tomography
CV	Cardiovascular
CVD	Cardiovascular Disease
DASI	Duke Activity Status Index
DLW	Doubly Labelled Water
DMMS	Dialysis Morbidity and Mortality Study
DOPPS	Dialysis Outcomes and Practice Patterns Study
ECM	Extracellular Matrix
EE	Energy Expenditure
EMA	Ecological Momentary Assessment
ESA	Erthyropoiesis Stimulating Agents
FMD	Flow Mediated Dilation
GFR	Glomerular Filtration Rate
GPAQ	Global Physical Activity Questionnaire
HAP	Human Activity Profile

HD	Haemodialysis
HDL	High Density Lipoprotein
HGS	Hand Grip Strength
HR	Heart Rate
ICAM	Intracellular Adhesion Molecule
ICC	Intra-class Correlation Coefficient
ICF	International Classification of Functioning, Disability and Health
IPAQ	International Physical Activity Questionnaire
ISWT	Incremental Shuttle Walk Test
IQR	Interquartile Range
KDQOL-SF	Kidney Disease Quality of Life - Short Form
KDOQI	Kidney Disease Outcomes and Quality Initiative
KT	Kidney Transplant
LFE	Low Frequency Filter Extension
LOA	Limits of Agreement
LUSS	Leicester Uraemic Symptom Scale
LVH	Left Ventricular Hypertrophy
MAP	Mean Arterial Pressure
METs	Metabolic Equivalents
MCS	Mental Component Score
MMP	Matrix Metalloprotease
MOS-SF 36	Medical Outcomes Short Form 36
MS	Metabolic Syndrome
MVC	Maximum Voluntary Contraction
MVPA	Moderate to Vigorous Physical Activity
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
PA	Physical Activity
PAD	Peripheral Arterial Disease
PASE	Physical Activity Scale for the Elderly
PCS	Physical Component Summary
PD	Peritoneal Dialysis
PF	Physical Function
PP	Pulse Pressure
PWV	Pulse Wave Velocity

ROC	Receive Operating Characteristic
RRT	Renal Replacement Therapy
SD	Standard Deviation
SPPB	Short Physical Performance Battery
SPSS	Statistical Package for Social Science
STS 5	Sit-to-stand 5
TPA	Total Physical Activity
TUAG	Timed Up and Go
URR	Uraemic Solute Removal
VC	Vascular Calcification
VO_{2max}	Maximum Oxygen uptake
VSMC	Vascular Smooth Muscle Cell
6MWT	Six Minute Walk Test
7DR	Stanford Seven Day Recall

Chapter 1: General Introduction and Literature Review

1.1 Introduction and background

Chronic kidney disease (CKD) is a long term condition in which the ability remove waste solutes, regulate fluid volume and electrolyte balance, and produce erythropoietin necessary for red blood cell production is irreversibly degraded. This condition is classified according to five stages of progressive organ impairment defined by thresholds of glomerular filtration rate (GFR) (table 1.1). Chronic kidney disease stage 5 represents the most severe stage, and is defined as little or no residual kidney function (<15 ml/min/1.73m^2), at which point survival is dependent on renal replacement therapy (RRT) (National Kidney Foundation 2002).

Table 1.1 Stages of CKD according to severity of kidney impairment.

CKD Stage	GFR*	Description
1	>90	Normal kidney function but urine findings or structural abnormalities or genetic trait indicate kidney disease.
2	60 - 89	Mildly impaired kidney function, and other findings (as for stage 1) indicate kidney disease.
3A	45 - 59	Moderately impaired kidney function
3B	30 - 34	
4	15 - 29	Severely impaired kidney function
5	<15 or dialysis	Very severe impairment, or 'established renal failure'.

*GFR values are normalised to a surface area of 1.73 m^2 (The Renal Association 2009).

Of the three treatment options available for RRT (peritoneal dialysis, haemodialysis, kidney transplant) haemodialysis (HD) therapy is the most common first modality (USRDS 2010; SRRR 2011; UKRR 2012). Maintenance HD is typically four to five hours in duration and provided in a hospital setting thrice weekly. Although renal transplants have increased, 42% of the prevalent stage 5 CKD population continue with maintenance HD, a proportion unchanged over the last decade (SRRR 2013). Haemodialysis is likely to remain a lifelong therapy for many individuals.

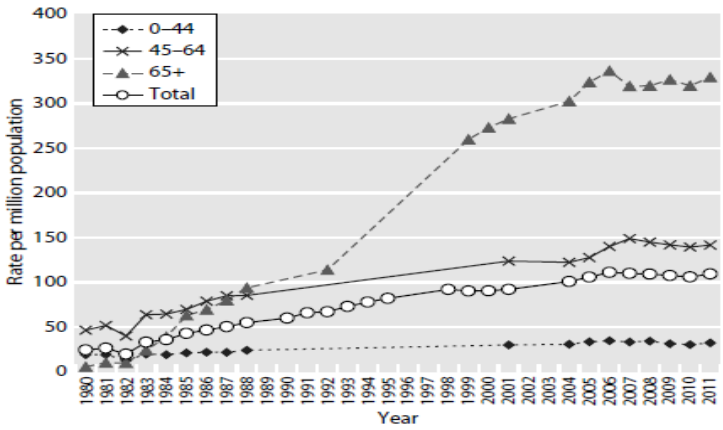
1.1.1 Prevalence and health burden of chronic kidney disease

It is estimated that prevalence of stages 3 to 5 CKD is 6% in the UK population (Roderick et al. 2011) and 10 - 16% for all stages of impairment worldwide making this condition a global health problem (Hallan et al. 2006; Coresh et al. 2007; Couser et al. 2011). Approximately 55,000 people in the UK currently receive RRT, of who 4,501 are Scottish residents (SRRR 2013). Alarmingly, annual incidence of

RRT in Scotland has more than doubled from 41 to 101 per million population since 1983 (SRRR 2013). Projected yearly population growth of around 5% is forecast for the UK (UKRR 2010) and North America (USRDS 2010). Not only is HD therapy the most common mode of RRT, it is also the most expensive in developed countries (Salonen et al. 2007; Just et al. 2008; Arrieta et al. 2011). The average cost of UK hospital based HD therapy per person has been calculated at £35,023 (Baboolal et al. 2008). Although people with stage 5 CKD represent less than 0.01% of the UK NHS patient population 3% of its annual budget is devoted to RRT (UKRR 2010). Similarly, in North America RRT accounts for 5.9% of Medicare expenditure (26.8 billion USD) with the majority devoted to HD (USRDS 2010).

Historically, glomerulonephritis, multisystem diseases, interstitial nephropathies have been the predominant primary renal diagnoses. However, stage 5 CKD is increasingly being driven by a rising tide of diabetes which has increased more than threefold over the last 30 years and now accounts for at least a quarter of primary renal diagnoses (USRDS 2012; UKRR 2012; SRRR 2013). In addition the last three decades have witnessed a dramatic shift in age demographic as the incidence rate for RRT acceptance among older adults (>64 years) has ballooned since 1980 (figure 1.1). Median age of the HD population is now around 65 years (UKRR 2012; SRRR 2013), with men accounting for 63% of those starting RRT (UKRR 2012).

Figure 1.1 UK RRT incidence rate from 1980 to 2011 (UKRR 2012).

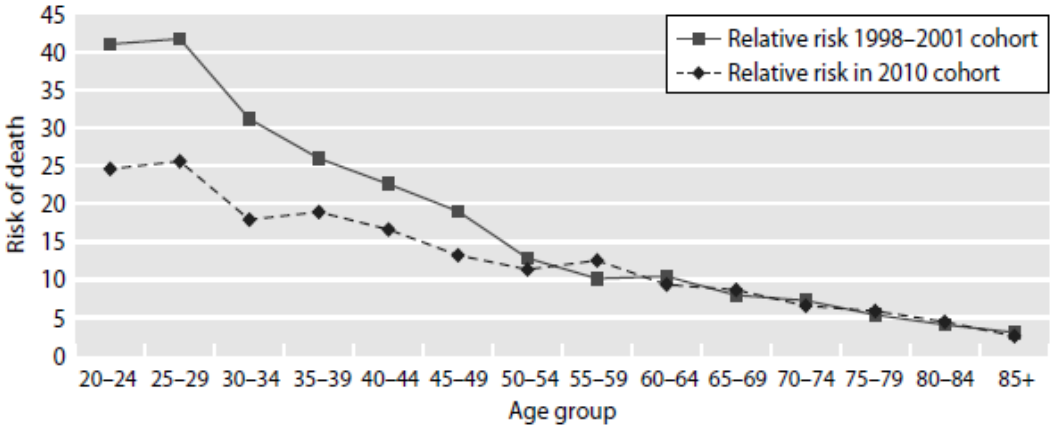


1.1.2 Life expectancy in stage 5 CKD

Maintenance HD for stage 5 CKD is life-saving, however longevity is still considerably reduced compared to non-uraemic peers. Illustratively, average life expectancy for an asymptomatic 55 year old in the UK is 26 years, but just five

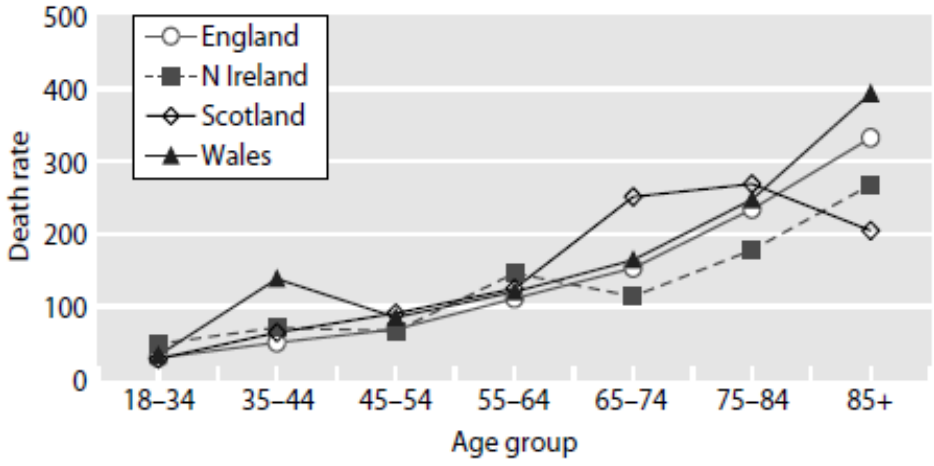
years for a person receiving dialysis therapy in Scotland (SRRR 2010). This disparity is even more profound for younger adults who experience an alarming 18 fold relative reduction in life expectancy (figure 1.2) compared to non-uraemic individuals (UKRR 2012).

Figure 1.2 Relative risk of death for prevalent RRT population compared to the general population (UKRR 2012).



First year survival rates for the dialysis population have continued to improve incrementally, however five-year survival rate remains as low as 35% (Breidhardt et al. 2011; UKRR 2012; USRDS 2012; SRRR 2013). Such statistics are a sobering reminder that despite advances in medical management, living with stage 5 CKD and HD therapy is still a fragile existence. Moreover UK renal registry data indicate mortality rate among older adults receiving HD in Scotland are significantly higher compared to the rest of the UK (figure 1.3).

Figure 1.3 Mortality rate per 1000 patients years by UK country and age group for prevalent dialysis patients (UKRR 2012).



1.1.3 Cardiovascular health and mortality in stage 5 CKD

Shorter life expectancy in this clinical population is mediated largely by cardiovascular (CV) causes. Disproportionately high CV morbidity and mortality in this population is largely attributed to increased stiffness of central and conduit arteries (London et al. 2011; Verbeke et al. 2011). Adverse haemodynamic consequences of large artery stiffening include widening of pulse pressure and isolated systolic hypertension (O'Rourke and Hashimoto 2007). In the CKD population this invariably leads to left ventricular hypertrophy (LVH) (Marchais et al. 1993; Nitta et al. 2004; Wang et al. 2007), and reduced coronary perfusion during diastole (O'Rourke and Hashimoto 2007). These outcomes are all independent predictors of CV morbidity and mortality of HD patients (Silberberg et al. 1989; Parfrey et al. 1996; Iseki et al. 1997).

1.1.4 Risk factors for CVD in stage 5

Vascular aging is accelerated in people with stage 5 CKD (Pannier et al. 2005; Sigrist et al. 2007; Suzuki et al. 2011), and it is believed this is due to greater burden of traditional and non-traditional CV risk factors (Zoccali 2000; UKRR 2012). Level of physical activity (PA) and cardiorespiratory fitness (CRF) are important CV and all cause mortality risk factors (Blair et al. 2001) and are similarly implicated in survival of HD patients. Individuals starting HD who are sedentary, frail or report severe difficulties with moderate activities are most at risk of poor outcomes (O'Hare et al. 2003; Stack et al. 2005; Johansen et al. 2007). Equally, higher levels of PA and a fitness level sufficient to walk up a moderate incline significantly ameliorate mortality risk in this population (Sietsema et al. 2004; Stack et al. 2005; Tentori et al. 2010). Worryingly, the dialysis population is characterised by high prevalence of low PA and CRF (Stack et al. 2005; Parsons and King-van Vlack 2009; Painter et al. 2011).

1.1.5 Health management in stage 5 CKD

Haemodialysis therapy for stage 5 CKD can prolong life and ameliorate some of the symptoms associated with this condition. However, there are indications that commencement of HD also coincides with a decline towards frailty (Johansen et al. 2010a), which is also predictive of poor short-term prognosis (Johansen et al. 2007). In light of their robust associations with health outcomes, routine monitoring of physical function and encouragement of PA by all nephrology staff is recommended by the Kidney Disease Outcomes and Quality Initiative (KDOQI) as part of health management (National Kidney Foundation 2005). However, PA counselling

practices among renal healthcare providers remain inconsistent (Delgado and Johansen 2010). This could reflect low awareness, but it may be difficult to operationalise recommendations when there is little information to support renal healthcare providers on how they may be implemented. There is a pressing need for clear guidance in this stagnant area of health management.

1.1.6 Monitoring physical activity and physical function in stage 5 CKD

Selection of the most useful assessment instruments to monitor PA and level of physical function is hampered by the bewildering array of subjective and objective outcomes that have already been employed in the CKD literature. Questionnaires have been widely used to monitor PA due to their low cost and expediency but they have recognised limitations. Consequently, participant mounted activity monitors that objectively estimate activity are increasingly being adopted in CKD health research for PA surveillance, however data reduction criteria are infrequently stated. Variable compliance with monitor wear has been observed in PA studies (Rich et al. 2013), therefore minimum wear time recommendations are necessary to ensure data are sufficiently reliable for meaningful analysis (Baranowski et al. 2008).

Importantly, wear criteria need to be stringent enough to ensure data integrity while at the same time allowing retention of an adequately representative sample (Catellier et al. 2005; Hinkley et al. 2012). Moreover, there are indications that wear time requirements for clinical populations characterised by low PA differ to current recommendations developed in samples of asymptomatic adults (Chen et al. 2009; Miller et al. 2013). Reliable characterisation of PA is crucial to enable clinicians to identify individuals at risk of poor outcomes and for investigators exploring behaviour and health outcomes in CKD. In addition, given the implications for analyses and conclusions, which form the basis of health recommendations, research to inform activity monitor data reduction criteria in stage 5 CKD is strongly indicated.

A single question regarding exercise frequency is prognostic of mortality among dialysis patients (O'Hare et al. 2003; Tentori et al. 2010). However, PA data obtained via activity monitors provide greater information density regarding behaviour indices and patterns. Moreover, they are better able to estimate activity at the lower end of the spectrum where many clinical populations tend to operate as well as quantify sedentary time, which is now a putative health risk factor independent of PA (Owen et al. 2010; Thorp et al. 2011). Physical activity is a

burgeoning area of research in CKD but there is little uniformity of activity monitors employed and few data from clinical populations to guide device selection. In addition, a considerable amount of PA data has been obtained via self-report questionnaires already. It would be advantageous to determine whether this bank of information could be meaningfully synthesised with data obtained via contemporary objective PA assessment methods. Research in this area is warranted in order that recommendations can be made regarding utility and standardisation of PA assessment instruments appropriate to outcomes of interest.

Routine monitoring of physical function (PF) is a KDOQI recommendation but there is limited guidance as to how this may be achieved. Cardiorespiratory fitness determined via cardiopulmonary exercise test is predictive of survival across the CKD trajectory (Sietsema et al. 2004; Gulati et al. 2012) but is not feasible as a routine outcome and may not adequately indicate functional limitations. Physical performance tests that replicate common activities (chair stands, walk tests) provide more feasible proxy measures of fitness and strength in the clinical setting and are predictive of mortality, falls, hospitalisations and dependency in asymptomatic older adults (Buatois et al. 2008; Tiedeman et al. 2008; Braden 2012). Functional mobility testing is similarly predictive of health outcomes (bone fractures, mortality, dependency) in the CKD population (Jamal et al. 2006, Cook and Jassal 2008; Roshanraven et al. 2013). An important 'person centred' perspective of an individual's level of function can be obtained by questionnaires, which have prognostic utility comparable to or better than clinical biomarkers of health status in stage 5 CKD (DeOreo et al. 1997; Lowrie et al. 2003; Knight et al. 2003; Mapes et al. 2003). There is now growing awareness of the prognostic utility of PF and its contribution to frailty (Fried et al. 2001). Consequently, there is a pressing need to identify the most useful PF outcomes to support healthcare providers in nephrology with implementation of KDOQI recommendations and current government health strategies.

Augmentation index (AI) and aortic pulse wave velocity (PWV) are commonly used as indicators of increased arterial stiffness, which is implicated in premature mortality of people with stage 5 CKD. Both vascular indices are associated with LVH (Marchais et al. 1993; Nitta et al. 2004) and have prognostic utility in the stage 5 CKD population (London et al. 2001a; Blacher et al. 2003; Verbeke et al. 2011). Importantly, accumulating evidence indicates PA that improves or maintains CRF attenuates vascular stiffening of non-uraemic adults of all ages (Vaitkevicius et al.

1993; Tanaka et al. 2000; Boreham et al. 2004; Gando et al. 2010b; Aoyagi et al. 2010). Physical activity and CRF are implicated in longevity of HD patients and form part of KDOQI recommendations for CV health management. However, the relationship between PA, CRF and arterial stiffness in this population has received little attention. Exploration in this area would seem a prerequisite for structured PA interventions aimed at reducing CV mortality and morbidity. In addition, although AI and PWV both measure arterial stiffness they are not interchangeable (Laurent et al. 2006; Sharman et al. 2009). Guidance regarding whether one or both outcomes are most appropriate for stage 5 CKD would be timely given that arterial stiffness is now being employed as an intermediate endpoint in studies targeting vascular health.

1.1.7 Summary

Despite medical advances people living with stage 5 CKD and maintenance HD experience shorter life expectancies. Encouraging PA and monitoring physical function are recognised as important in augmenting health management in stage 5 CKD. However, the literature shows little uniformity of assessment methods and even less exploration of their clinical utility. Although PA and CRF are implicated in survival of HD patients there is a paucity of data regarding their relative contribution to arterial stiffness an important CV risk factor. Exploration of these relationships may also help inform timely selection of the most appropriate index of arterial stiffness for the stage 5 CKD population. The overarching aims of this project are to:

- Provide substantive recommendations to support healthcare providers and investigators with informed selection of PA and PF assessment instruments that reflect the current shift towards to 'person-focused' care.
- Explore whether lower mortality observed with higher levels of PA and CRF is potentially mediated via a direct effect on arterial stiffness in this population.

1.2 Literature Review

1.2.1 Epidemiology of physical activity in stage 5 CKD

1.2.1.1 Prevalence of low physical activity in stage 5 CKD

There is general agreement from a large body of studies that low levels of physical activity (PA) are highly prevalent among people with stage 5 CKD (table 1.2). Early research indicated 59% were not capable of PA more strenuous than basic ADLs (Painter et al. 2001) a statistic that appears to have changed very little. Large-scale epidemiological studies such as the Dialysis Mortality and Morbidity Study (DMMS) and the more recent international Dialysis Outcomes and Practice Patterns Study (DOPPS) agree that 56% to 63% of dialysis patients exercised once a week or less (O'Hare et al. 2003; Stack et al. 2005; Tentori et al. 2010). Worryingly, this figure appears to be higher (75%) among women receiving HD (Winkler et al. 2002). These findings are consistent with pooled accelerometry data from single centre studies in different countries that classified almost two thirds of HD patients as sedentary or low-active (Cupisti et al. 2011; Avesani et al. 2012).

Just 14% of incident HD patients in the Choices for Healthy Outcomes in Caring for ESRD Study reported exercising three or more times per week (Longenecker et al. 2002). Smaller cohort studies, using non-standardised questionnaires (Painter et al. 2000; Allen and Gappelmaier 2001) found that even fewer patients (10.4% to 12%) met contemporary exercise guidelines, with exercise frequency even lower for female HD patients (Allen and Gappelmair 2001; Nielens et al. 2001; Brenner and Brohart 2008; Sridharan et al. 2013) as observed in the general population (Townsend et al. 2012). Although exercise frequency is predictive of survival in stage 5 CKD (O'Hare et al. 2003; Stack et al. 2005; Tentori et al. 2010) it does not accurately characterise other aspects of habitual PA that may also endow health protective benefits (Ainsworth et al. 2011). Furthermore, exercise is often used interchangeably with PA. Although both terms involve movement and energy expenditure above basal metabolic rate, exercise is a subcategory of PA and is defined as: "Physical activity that is planned, structured, repetitive and purposive in the sense that the improvement or maintenance of one or more components of physical fitness is the objective" (Caspersen et al 1985, p. 128). More recent studies employing standardized questionnaires found just 18.6% to 25.5% of patients met consensus PA guidelines of 150 minutes of moderate to vigorous physical activity (MVPA) on most days of the week (Wong et al. 2011; Stringuetta-Belik et al. 2012).

Table 1.2 Physical activity level of maintenance haemodialysis patients estimated via subjective and objective methods.

Study	Sample (n)	M/F %	Age	PA measure	Physical activity findings
Sridharan et al. 2013	Prevalent HD (n = 166)	58/42	62.0 ± 15.5	Stanford 7 day recall	Activity kcals/day: men 761 ± 315 women 588 ± 201 23%↓(p < 0.001) Total kcals/day: men 2440 ± 590 women 1976 ± 452 (p < 0.001).
Matsuzawa et al. 2012	Prevalent HD (n = 202)	48/52	64 (57 - 42)	Lifecorder uniaxial accelerometer (waist mounted)	Median total PA mins/day: 42.7 (22.8, 65.8), Median steps/day: 3925 (2287, 6284).
Avesani et al. 2012	Prevalent HD (n = 134)	64/36	54.9 ± 15.9	SenseWear™ Armband	Average daily physical activity outcome values: Total kcal/day 1938 ± 437; Activity related kcal/day 289 (0; 1793); Steps 5660 (73; 16565), MET/day 1.39 ± 0.2. 45% classed as sedentary (< 5000 steps/day) Physical activity outcome values: dialysis vs non-dialysis days Total kcals/day: 1864 ± 408 vs 1985 ± 484 ↓6% (p = 0.001) PA related kcal/day: 202 (0, 1152) vs 303 (0, 2113) ↓33% (p = 0.001) Steps/day: 4620 (77, 13 957) vs 5544 (72, 18 220) ↓17% (p = 0.001) MET/day: 1.33 ± 0.2 vs 1.42 ± 0.3 ↓6% (p = 0.001).
Stringuetta-Belik et al. 2012	Prevalent HD (n = 102)	55/45	58.7 ± 15.1	International Physical Activity Questionnaire	Participants categorised: active (25.5%), irregularly active (34.3%), inactive/sedentary (40.2%).
Wong et al. 2011	Prevalent HD (n = 70)	59/41	57.0 ± 12.5	Global physical activity questionnaire (WHO 2009)	81.4% of participants categorised as low active (18.6%) moderately active.
Painter et al. 2011	Prevalent HD (83%), PD (10.1%), Transplant 6.8% (n = 1323)	56/44	62.4 ± 15.2	Questionnaire on frequency, duration, intensity of habitual physical activity	57% reported themselves 'regularly active'. 13.2% met PA health guidelines for frequency, duration, intensity. Diabetic participants least likely to meet PA guidelines.
Baria et al. 2011	Prevalent HD (n = 32) Healthy sedentary controls (n = 22).	63/37	46.3 ± 12.2	Sensewear Pro2 Armband monitor biaxial accelerometer. Physical activity scale for the elderly (PASE)	Physical activity outcome values: dialysis vs non-dialysis days Steps/day: 7094 ± 2436 vs 8961 ± 3346, ↓21% (p < 0.01) Total kcal/day: (2096 ± 324 vs. 2265 ± 413, ↓7.5%(p < 0.01) Activity kcal/day: 278.7 (9.5, 1145) vs 364.5 (90, 1828), ↓24% (p < 0.01) PA counts/day: 6599 ± 1503 vs. 7236 ± 1767, ↓9% (p = 0.05). MET/day: 1.4 ± 0.3 vs. 1.5 ± 0.3, ↓7% (p < 0.01) Comparison subgroup HD patients vs sedentary controls (n = 22) HD steps/day 7,425 ± 2,567 vs 10,427 ± 1,988 ↓29% (p < 0.01) PA counts: 6,709 ± 1,179 vs 8,140 ± 679. ↓18% (p < 0.01) Total kcal/day: 2,111 ± 268 vs 2,514 6 307 ↓16% (p < 0.01) Activity kcal/day: 303 (76 to 1,251) vs 565 (214 to 1,319) ↓46% (p<0.01) MET/day: 1.38 ± 0.26 vs 1.52 ± 0.14 (p = 0.09) PASE: 66 (3,181) vs 181 (3, 286), ↓74% (p < 0.01)

Study	Sample (n)	M/F %	Age	PA measure	Physical activity findings
Mafra et al. 2011	Prevalent HD (n = 24) Controls (n = 18)	75/25	67.0 ± 14.7 62.3 ± 15.3	Sensewear Pro2 Armband biaxial accelerometer	Steps/day: controls 8104 ± 5419; HD normal CRP 6016 ± 3752; HD with increased CRP 2801 ± 2754 (p = 0.001) Total kcal/kg/day: controls 31.8 ± 7.0, HD normal CRP (32.0 ± 6.7; HD with increased CRP 25.5 ± 4.1 (p = 0.012).
Cupisti et al. 2011	Prevalent HD (n = 50) Controls (n = 33)	64/36	59.0 ± 13.0	Sensewear Pro2 Armband biaxial accelerometer.	Comparison HD vs controls Mean daily METs: 1.3 ± 0.3 vs. 1.5 ± 0.2 ↓13% (p < 0.01) Mins/day in PA >3 METs: 89 ± 85 vs. 143 ± 104 ↓38% (p < 0.05) Steps/day: 5584 ± 3734 vs. 11,735 ± 5,130 ↓52.5% (p < 0.001) Total kcals/day: 2190 ± 629 vs. 2462 ± 443 ↓11% (p < 0.05) 62% defined as sedentary (< 1.4 METs/day).
Agarwal and Light 2011	Prevalent HD (n = 114) CKD 2-4 (n = 148) Controls (n = 19)	63/37 97/3 89/11	51.5 ± 11.4 69.0 ± 10.6 60.1 ± 10.0	Actiwatch 64 accelerometer (Wrist mounted)	Average percentage of day spent sedentary : HD 71%; CKD 66%; controls 56% (p < 0.0001).
Li et al. 2010	Prevalent HD (n = 187)	51/49	59 (IQ not stated)	International Physical Activity Questionnaire	Median MET minutes/week 1743 (0 - 13482). Inactive 26.7%, minimally active 73.3%.
Tentori et al. 2010 DOPPS	Prevalent HD & PD (n = 20920)	58/42	60.7 ± 14.8	Single question on exercise frequency	Severe difficulty with: vigorous PA = 69%; moderate PA = 38% Self reported exercise frequency: daily 14.1%, 4 - 5x/week 5.7%, 3x/week 17%; 1x/week 10.5%; < 1x/week 8.5%; never 43.9%.
Kutsuna et al. 2010	Prevalent HD (n = 153)	43/57	64.0 ± 11.0	Lifecorder uniaxial accelerometer	Average daily PA in activities > 1.8METs = 43.1 ± 29 mins/day.
Masuda et al. 2009	Prevalent HD (n = 35) Prevalent PD (n = 26)	69/31	58.3 ± 14.7 47.5 ± 14.2	Omron pedometer	Average steps/day: HD 3391 ± 2010 vs PD 6336 ± 4924.
Van den Ham et al. 2005	Prevalent HD (n = 18) Renal Transplant (n = 35) Controls (n = 21)	63/37 51/49 52/48	49.0 ± 11.9 52.3 ± 10.4 54.9 ± 10.8	Baecke Activity questionnaire	Sport activity HD 1.8 ± 0.6 v Transplant 2.2 ± 0.8 v Controls 2.5 ± 0.8 Total activity HD 6.2 ± 1.5 v Transplant 7.2 ± 1.5 v Controls 7.8 ± 1.4 Difference between HD and controls: Sport ↓28% Total ↓21% (p < 0.05).
Zamojska et al. 2006	Prevalent HD (n = 60) Controls (n = 16)	45/55 36/64	60 ± 13 56 ± 6	Pedometer (Oregon Scientific)	Average steps/day 3500 48 hour interdialytic stepcount: HD 6896 ±2357 vs controls 14181 ± 5383 ↓51% (p < 0.001).
Majchrzak et al. 2005	Prevalent HD (n = 20)	50/50	50.1 ± 9.9	Hip mounted RT-3 triaxial accelerometer	PA counts/day: dialysis 128279 ± 74009; non-dialysis 168744 ± 95168 (p = 0.025). dialysis day counts/day: diabetics 82397 ± 48,166; non-diabetic 152985 ± 74987 (p = 0.038); non-dialysis counts/day diabetics 85593 ± 40,054 versus 213,517 ± 85,633 (p < 0.001).

Study	Sample (n)	M/F %	Age	PA measure	Physical activity findings
Stack et al. 2005 O'Hare et al. 2003 DMMS Wave 2	Incident HD & PD (n = 2264)	54/46	58.0 ± 16	Single question on exercise frequency	Severe difficulty with: vigorous PA = 75%; moderate PA = 42% Self reported exercise frequency: Daily or almost daily 19.8%; 4 - 5x/week 5.5%; 2 - 3x/week 18.4%, about 1x/week 11.1%, <1x/week 10.0%; almost never or never 35.1%.
Sakkas et al. 2004	Prevalent HD (n = 12) Prevalent CAPD (n = 12)	83/17 58/42	61.7 ± 13.9 55.2 ± 10.9	Stanford 7 Day recall Questionnaire	Average total kcals/day: HD 2750 ± 600; CAPD 2750 ± 610.
Johansen et al. 2003a	Incident HD (n = 54)	67/33	51.7 ± 17	TriTrac-R3D triaxial accelerometer. Human activity profile 4 time measurement time points over 12 months	Triaxial activity counts declined 3.4%/month from baseline (p = 0.01). HAP maximum activity score declined 6 points/month (p = 0.025). **Note: 31 participants with 12 month follow up data.**
Longenecker et al. 2002 CHOICE study	Incident HD (73%) Incident PD (27%) (n = 1041)	54/46	57.8 ± 0.5	Two questions on exercise frequency long enough to elicit perspiration.	14% reported PA sufficient to elicit perspiration (≥ 5 METs) ≥ 3 times/week.
Winkler et al. 2002	prevalent HD (n = 44)	0/100	61.2 ± 10.3	Single yes/no PA question. "Do you exercise regularly"	75% reported not doing regular PA.
Nielens et al. 2001	Prevalent HD (n = 32)	38/62	45.9 ± 13.1	Pre-transplant PA Baecke Activity questionnaire Stanford 7-day recall	Comparison with norm values: Score: 5.9 ± 2.39 ↓22% (p < 0.05), Females 4.1 ± 2.27 ↓35% (p < 0.01) Total kcals/day: Males 2367 ± 499 ↓26% (p < 0.05), Females 1869 ±367 ↓18% (p < 0.01).
Allen and Gappelmaier 2001	Prevalent HD (n = 135)	58/42	56.0 ± 17.0	Three questions on exercise habits	60% exercised > 1 x/week. 10.4% expended > 1000 kcal/week in exercise. Males more active. No females met exercise EE requirement
Johansen et al. 2000	Prevalent HD (n = 34) Sedentary controls (n = 80)	65/35	51.5 ± 3.0	TriTrac-R3D triaxial accelerometer. Stanford 7 day recall	PA counts/day: HD 104,718 ± 9631 vs controls 161,255 ± 6792 controls. ↓ 35% CI: 20 to 50% (p < 0.0001) ↑difference with advancing age (15% at 30 yrs to 57% at 70 yrs). 7DR calculated kcal/kg/day: HD 33.6 ± 0.5 vs controls 36.2 ± 0.5 ↓7% (p = 0.002).
Painter et al. 2000	Prevalent HD (n = 286)	43/57	55.9 ± 15.2	Self-report. PA categorisation: 1- ADLs only; 2- stretches & strengthening; 3-some exercise but less than recommendations; 4-achieving exercise guidelines	59% reported no PA above basic ADLs. 12 % reported exercising at recommended levels for maintaining CV health.

A larger cohort study indicated that this could be as low as 13.2% (with diabetics even less active) despite 57% of respondents perceiving themselves to be regularly active (Painter et al. 2011). Similarly low levels of PA are reported in smaller studies employing objective measures. Average daily step counts, activity counts, minutes of MVPA, and activity related energy expenditure (EE) are 18% to 52.5% lower than those observed for age matched individuals without CKD (Johansen et al. 2000; Zamojska et al. 2006; Baria et al. 2011; Cupisti et al. 2011; Mafra et al. 2011). Notably, habitual PA of HD patients is even lower (18% to 46% depending on outcome) than sedentary non-uraemic peers (Johansen et al. 2000; Baria et al. 2011). Furthermore, this disparity widens with advancing age (Johansen et al. 2000), systemic inflammation and diabetes (Majchrzak et al. 2005; Mafra et al. 2011). Notably, the average activity related EE among HD patients is just 15% of the total daily amount (similar to thermogenic effect of diet) compared to 24% for sedentary controls (Baria et al. 2011). Steps taken are often below 4000 per day (Masuda et al. 2009; Nowicki et al. 2010; Matsuzawa et al. 2012), which is consistent with other chronic conditions including: heart failure; peripheral arterial disease; chronic obstructive pulmonary disease; cerebrovascular accident (Tudor-Locke et al. 2009b; Tudor-Locke et al. 2011a).

1.2.1.2 Influence of haemodialysis on physical activity behaviour

Low PA in the HD population is mediated at least in part by periods of enforced sitting while dialysis takes place. Objectively estimated indices of PA such as step count, activity related EE and activity counts are 17% to 37% lower on dialysis days compared to non-dialysis days (Majchrzak et al. 2005; Baria et al. 2011; Avesani et al. 2012). Behaviour is influenced beyond the HD period with PA in the two hours immediately after dialysis higher than the same epoch on non-dialysis days but significantly lower by hour four (Majchrzak et al. 2005). Worryingly, objectively estimated PA declines at a rate of 3.4% per month after initiation of HD therapy (Johansen et al. 2003a). Moreover, there are indications that HD negatively influences PA to a greater extent compared to other RRT modalities. Average daily stepcount for HD patients is almost half that of peritoneal (PD) dialysis patients (Masuda et al. 2009) while PA of transplant recipients is not significantly different to controls (van den Ham et al. 2005) or norm values (Nielens et al. 2001).

Increased sedentary behaviour is precipitated by commencement of HD therapy but there is a paucity of data regarding this metric in stage 5 CKD. Wong et al. (2011)

reported seated time of their HD patients descriptively, but did not express this outcome as a percentage of waking hours. An accelerometry study revealed maintenance HD patients spent a significantly greater percentage of their day sedentary (71%) compared to people with stage 2 - 4 CKD (66%) (Agarwal and Light 2011). Moreover, HD patients in the cited study spent almost 30% more of their waking hours sedentary compared to asymptomatic participants of more advanced age in the 2003 - 2004 National Health and Nutrition Examination Survey (NHANES) (Matthews et al. 2008). This observation is particularly noteworthy in light of accumulating evidence linking seated time with health outcomes.

Figure 1.4 'Couch potato' / 'hospital potato'.

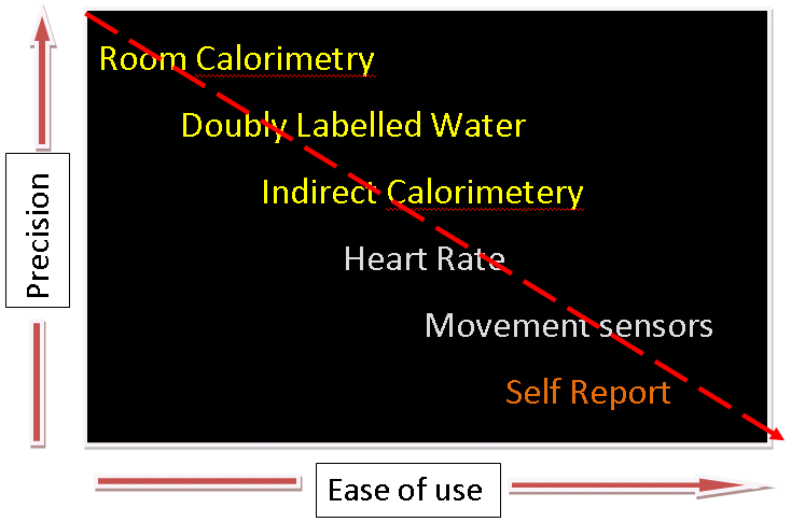
(Smith 2014, with permission (left); Huggins 2007 (right))

A preponderance of studies indicate that people undergoing maintenance HD for stage 5 CKD have lower levels of PA compared to the general population. Importantly however, findings from these studies are based on data from self selected volunteers. Large epidemiological studies such as the DMMS (O'Hare et al. 2003) excluded a significant percentage (12.5%) of enrolled stage 5 CKD participants who were unable to transfer or ambulate and over a third more (37%) due to missing PA data. Latterly excluded participants were characterised by being slightly older, more likely to be malnourished and receiving HD therapy all factors associated with lower PA. Furthermore, other studies excluded potential candidates that required assistive aids for ambulation (Kutsuna et al. 2010; Matsuzawa et al. 2012). Consequently, the actual prevalence of low PA in the wider stage 5 CKD population as reported in the current literature is likely under-represented.

1.2.1.3 Physical activity counselling practices in stage 5 CKD

In light of the high prevalence of low PA and sedentary behaviour among maintenance HD patients, and well documented associations with a range of health outcomes there is a compelling case for routine monitoring of these behaviours. Importantly, section 14.2 of the KDOQI guidelines recommends "all dialysis patients should be counselled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity" (National Kidney Foundation 2005, p. S60). Despite this recommendation Painter et al. (2011) found that while 57% of people with stage 5 CKD had "been talked to about exercise" only 34% had received literature on initiating physical activity. Disturbingly, an earlier multi-centre survey found that over 60% of healthcare providers did not assess the exercise patterns or recommend appropriate exercise programmes for people with stage 5 CKD (Johansen et al. 2003b).

Figure 1.5 Physical activity assessment methods - precision and ease of use.



1.2.1.4 Overview of physical activity assessment

A spectrum of methods is available to estimate habitual PA, which trade varying levels of measurement precision for expediency and cost (figure 1.5), with selection dependent on intended purpose. Subjective estimates of PA obtained via self-report questionnaires have been widely employed in health research due to expediency and low cost. However, questionnaire responses may be influenced by education level, cognition, gender, social desirability, and are susceptible to measurement error such as misreporting of PA volume (Bonnefoy et al. 2001; Washburn et al. 2003; Mahabir et al. 2006) and misclassification of PA intensity (Arroll and

Beaglehole 1991; Sallis and Saelens 2000). The most precise measures of PA are obtained via 'gold standard' techniques such as doubly labelled water and calorimetry but these methods carry significant burden of time, expense, and specialised personnel to administer. Devices such as heart rate (HR) monitors and participant mounted motion sensors are more feasible methods of objectively quantifying PA. Moreover, they can capture behaviour patterns as well as important PA parameters such as steps taken, time seated and epochs of PA at various levels of intensity, which 'gold standard' methods cannot.

1.2.1.5 Objective estimation of habitual physical activity in stage 5 CKD

In light of recognised limitations of PA questionnaires there has been a shift towards using objective PA assessment methods for CKD health research over the last 15 years. A third of the 51 located PA studies undertaken in stage 5 CKD (up until 2013) have used objective methods but HR monitoring has thus far not been employed as an activity proxy. Although HR can indicate PA intensity and patterns, this method is influenced by dietary thermogenesis, emotions, ambient temperature, variability of HR response and heart pacing medications/devices (Freedson and Miller 2000; Janz 2002). In addition, concordance studies with accelerometry conclude HR monitoring has lower utility in estimating light PA (MacFarlane et al. 2006; Manohar et al. 2013).

Pedometry, which has been frequently employed in epidemiological research (Tudor-Locke et al. 2009a) was used in four stage 5 CKD health studies (table 1.3). As well as being relatively cheap and expedient, pedometry has clinical utility with respect to PA stratification and health outcomes. Thresholds of <5000 steps/day and >8000 steps/day may be employed to classify individuals as sedentary (Le Masurier et al. 2003; Tudor-Locke et al. 2009a) and those likely to be achieving PA guidelines respectively (Tudor-Locke et al. 2009a). Notably, a cutpoint of <4040 steps/day is associated with low serum concentration of high density lipoprotein (<1.03 mmol/L) among HD patients which is predictive of increased CV risk (Masuda et al. 2009). Moreover, incremental increases of 1000 steps/day are independently associated with statistically significant reductions in blood pressure of women with type 2 diabetes (Manjoo et al. 2010) and a 10% lower risk of metabolic syndrome among middle-aged adults (Sisson et al. 2010).

A limitation of pedometers however is that they do not provide specific data regarding activity patterns, epochs at a given PA intensity or time spent inactive.

Moreover, although walking is the most common manifestation of daily PA, the metric of steps taken excludes other activity modalities such as swimming, cycling and resistance exercise. In addition there is general agreement from laboratory and free living studies that accuracy of pedometers declines markedly with slower gait (Tyo et al. 2011; Feito et al. 2012) and in overweight and obese individuals (Crouter et al. 2005). Importantly, gait speed declines with advancing age and reduced lower limb muscle strength (Bohannon 1997). Consequently, these devices may be inappropriate for use in stage 5 CKD, which is characterised by advanced average age and reduced physical function.

1.2.1.6 Accelerometers and physical activity surveillance in stage 5 CKD

Conceptually, motion sensors that convert body accelerations into activity counts are suggested to be better suited to estimating PA and are increasingly being employed. However, there is little uniformity regarding type of accelerometers employed for PA monitoring in the CKD literature. Five different accelerometers, which detect movement via uniaxial (Lifecorder, Actiwatch 64), biaxial (Sense Wear Pro2 Armband) and triaxial configurations (TriTrac-R3D, RT-3 Triaxial Research Tracker) have been employed in studies involving people with stage 5 CKD (table 1.3). Multiaxial accelerometers capture movement in a greater number of planes compared to uniaxial devices, and are thus believed to offer greater sensitivity to detection of light activities. Accelerometers convert body accelerations into activity counts which can be categorised into categories of PA intensity by most of these devices, however only the SenseWear Armband offers a stepcount output.

In addition to diversity of accelerometer methods used to monitor behaviour in the HD population the PA literature shows a remarkable lack of uniformity regarding data reduction methods (table 1.3). This further compounds the problems faced by investigators wishing to compare results and pool PA data for further analysis. Studies vary widely in the number and type of days monitored (ie: dialysis, non-dialysis, and weekend), often with no stated rationale. Monitoring protocols for pedometry studies vary from seven days (Ota et al. 1997; Masuda et al. 2009), to 48 hours during mid-week and a weekend (Nowicki et al. 2010), to just two inter-dialytic days (Zamojska et al. 2006). Accelerometer studies in stage 5 CKD tend to adopt a seven-day monitoring protocol (table 1.3), which is a commonly prescribed period in health studies (Kristensen et al. 2010; Colley et al. 2011; Feinglass et al. 2011; Tudor-Locke et al. 2011b; Esliger et al. 2012).

Table 1.3 Objective physical activity assessment methods employed in stage 5 CKD.

Study	Sample	Age	Objective measure	Monitoring period	Data reduction criteria
Ota et al. 1997	Prevalent female HD patients (n = 41)	61 ± 16	Pedometer/calorie counter (Suzuken)	7 days, waking hours.	Not stated.
Johansen et al. 2000	Prevalent HD (n = 34) Sed' controls (n = 80)	51.5 ± 3.0	TriTrac-R3D accelerometer	7 days, waking hours.	5 days wear. Valid wear day criterion not defined.
Johansen et al. 2001a Johansen et al. 2001b	Prevalent HD (n = 39)	52.0 ± 16.0	TriTrac-R3D accelerometer	7 days, waking hours.	5 days wear. Valid wear day criterion not defined.
Hung et al. 2002	Prevalent HD (n = 47)	50.3 ± 16.7	TriTrac-R3D accelerometer	7 days, waking hours.	5 days wear. Valid wear day criterion not defined.
Johansen et al. 2003a	Prevalent HD (n = 54)	51.7 ± 17.0	Not stated	Not stated.	Not stated.
Majchrzak et al. 2005	Prevalent HD (n = 20)	50.1 ± 9.9	RT-3 Triaxial Research Tracker (hip mounted)	7 days, waking hours.	5 days wear (2x dialysis & 2x non-dialysis days minimum). Valid wear day criterion not defined.
Zamojska et al. 2006	Prevalent HD (n = 60)	60.0 ± 13.0	Pedometer (Oregon Scientific)	2 mid-week interdialytic days.	Not stated.
Masuda et al. 2009	Prevalent HD (n = 35)	58.3 ± 14.7	Omron pedometer	7 days, waking hours.	Not stated.
Kutsuna et al. 2010	Prevalent HD (n = 153)	64.0 ± 11.0	Lifecorder accelerometer	7 days, waking hours.	Not stated.
Nowicki et al. 2010	Prevalent HD (n = 33)	58.3 ± 10.1	DT1845SW Pedometer (Shenzhen)	48 hours between mid-week dialysis sessions and inter-dialytic weekend period.	Not stated.
Gordon et al. 2011	Prevalent HD (n = 26)	55 ± 13	TriTrac-R3D accelerometer	1x dialysis and 1x non-dialysis day.	Not stated.
Agarwal & Light 2011	Prevalent HD (n = 114) CKD 2-4 (n = 148) Controls (n = 19)	51.5 ± 11.4 69.0 ± 10.6 60.1 ± 10.0	Actiwatch 64 (wrist mounted)	HD 2 interdialytic days. CKD 7 days Controls 7 days.	Not stated. Wrist monitor reactivity.
Mafra et al. 2011	Prevalent HD (n = 24) Controls (n = 18)	67 ± 14.7 62.3 ± 15.3	Sense Wear Pro2 Armband accelerometer	7 days, 24 hours continuous.	Minimum wear time of ≥95%.
Baria et al. 2011	Prevalent HD (n = 32)	46.3 ± 12.2	Sense Wear Pro2 Armband accelerometer	7 days, 24 hours continuous.	Minimum wear time of >90% (2x dialysis, 2x non-dialysis, 1x weekend day minimum)
Cupisti et al. 2011	Prevalent HD (n = 50) Controls (n = 33)	59.0 ± 13.0	Sense Wear Pro2 Armband accelerometer	48 hour mid-week interdialytic period.	Not stated.
Matsuzawa et al. 2012	Prevalent HD (n = 202)	64 (57 - 72)	Lifecorder accelerometer	7 days, waking hours.	4 non-dialysis days. Valid wear day criterion not defined.
Avesani et al. 2012	Prevalent HD (n = 134)	54.9 ± 15.9	Sense Wear Pro2 Armband accelerometer	7 day, 24 hours continuous.	Minimum wear time of >90% (1 dialysis & 1 non-dialysis day minimum).

There is less consistency across studies regarding minimum wear days for inclusion of participant PA data. Studies using triaxial accelerometers (TriTrac R3D, RT3 Research Tracker) show some agreement in stating a minimum of five wear days but only Majchrzak et al. (2005) specified how many dialysis days. Overall however, there is no adherence to a minimum standard for number and type of days required for participant PA data inclusion. The majority of protocols employed a waking hour monitoring period with the exception of those employing the Sensewear Armband, which was worn for 24 hours/day (Baria et al. 2011; Mafra et al. 2011; Avesani et al. 2012). Notably, only studies using the latter defined a valid wear day (>90 to ≥95% wear for the 24 hour wear period) in contrast to the remaining studies, which did not state this aspect of data reduction. Importantly, observations from PA studies indicate not all participants will wear their accelerometer for the prescribed period despite reminders and incentives (Baranowski et al. 2008; Rich et al. 2013). In addition, monitor wear time during the day is usually discretionary and thus subject to variation both within and between participants (Hinkley et al. 2012). A remarkable unifying aspect of all PA studies undertaken with motion sensors in stage 5 CKD is that not one participant was excluded from final analyses due to insufficient accelerometer wear. Worryingly, it appears that the majority of PA studies in stage 5 CKD have not explicitly at least, taken into account intra- and inter-individual differences in wear time and their potential impact on reported outcome variables.

1.2.1.7 Reliability of objectively estimated physical activity outcomes

Guidance regarding minimum accelerometer wear time is crucial to ensure PA data are sufficiently reliable for final analyses so that the ability to detect relationships with other variables is not diminished (Baranowski et al. 2008). Measurement error negatively impacts statistical power to investigate PA mediated mechanisms influencing health and determine dose-response relationships that potentially form the basis of health recommendations (Schatzkin et al. 2009). Appropriate comparison and synthesis of pooled data from different PA studies is also more easily facilitated if standardised wear time guidelines are adopted to ensure data are reliable. Physical activity assessment may become an adjunct to traditional clinical indices of health status in the future. Therefore, reliable characterisation of PA is necessary to identify individuals at risk of poor outcomes, as well as monitor change in behaviour.

Investigators using accelerometers are faced with important methodological considerations regarding how many hours of wear constitute a 'valid' day and the number of days required to provide a reliable estimate of various PA indices (Masse et al. 2005; Troiano et al. 2008; Ojiambo et al. 2011). Given that PA patterns of HD patients vary according to the hour of day and day of the week (Majchrzak et al. 2005) wear time guidelines are necessary to quality assure accelerometer data. However, in so doing there is a trade-off between application of wear time criteria that are stringent enough to ensure data integrity while at the same time allowing retention of a sample size that is sufficiently large and representative for subsequent analyses (Catellier et al. 2005; Hinkley et al. 2012). Importantly, even small increases in stringency of wear time criteria can adversely affect sample size (Masse et al. 2005; Chen et al. 2009; Miller et al. 2013), thereby increasing sample bias by reducing representativeness and adversely affecting group estimates of PA and sedentary behaviour (Masse et al. 2005; Tudor-Locke et al. 2012; Herrmann et al. 2013; Toftager et al. 2013).

Statistically-based data imputation is one strategy that researchers may utilise to manage missing or incomplete PA data. Catellier et al. (2005) evaluated different algorithms according to type of 'missingness' for imputing incomplete PA data due to wear time inconsistencies. While it was observed that imputing data was never worse than deleting incomplete days, performance of the algorithms was adversely affected by a number of factors including larger proportion of missing data, lower correlation of PA across days of the week. Furthermore, the authors acknowledged there was no way of objectively determining whether data were 'missing at random', 'completely missing at random' or 'not missing at random'. This approach also assumes that episodes of missing data represent average PA.

1.2.1.8 Minimum required accelerometer wear time

An alternative to discarding incomplete participant PA data is to establish the minimum required accelerometer wear time that reliably reflects an individual's habitual PA and sedentary behaviour. The first part of this process is to determine inter-day variability of PA and sedentary behaviour indices via intra-class correlation coefficient (ICC) calculations (Baranowski and de Moor 2000). An ICC value of 1.0 for a given outcome indicates perfect reliability or repeatability with all variation observed to be between rather than within participants. Intuitively, the greater the variability of accelerometer estimated PA between days the higher the number of

monitor wear-days that will be required to reliably reflect an individual's habitual PA patterns.

Opinions vary regarding the reliability value that should be achieved in order to define a measurement as being reliable. Hicks (2005) argues that a clinically acceptable ICC should be higher than 0.60. In contrast a minimum ICC of 0.70 is recommended by Nunally (1978) to determine sufficient reliability of an outcome instrument while higher thresholds of 0.90 and 0.95 are recommended for groups and use at an individual level respectively. Vincent (2005) contends that values below a reliability level of 0.80 are questionable for physiological data and this threshold has been adopted as the standard in previous PA reliability studies (Trost et al. 2000; Penpraze et al. 2006). Accelerometer wear time recommendations for a chosen level of reliability are then calculated by applying the Spearman Brown Prophecy Formula (Stanley 1971) to the ICC.

There is agreement in the general literature that a monitoring period of three to five days is sufficient to objectively estimate PA of adults via accelerometry with a reliability level of 0.80 (Trost et al. 2005; Ward et al. 2005). Wear time recommendations of three and three to four days for minutes of total PA were reported in studies involving elderly and middle aged adults (Hart et al. 2011c and Matthews et al. 2002 respectively). Interestingly these reliability studies employed the same monitoring protocols of 21 consecutive days and uniaxial Actigraphs but chose markedly different cutpoints of >50 (Hart et al. 2011c) and >500 cpm (Matthews et al. 2002) for total PA. That their recommendations agree so closely suggests reliability of this PA index is stable regardless of cutpoint used. In addition Matthews et al. (2002) specified a minimum of 12 hours wear for a valid data, while this criterion was not explicitly specified by Hart et al. (2011c). If the latter study used all 21 days irrespective of daily wear period length it might suggest outcome reliability is less susceptible to the effects of minimum daily wear time compared to wear days as observed in studies of children (Penpraze et al. 2006; Mattocks et al. 2008).

A more stringent requirement of four to five days was recommended by Cook and Lambert (2008) for estimation of total PA despite using the same uniaxial accelerometer and cutpoint as Matthews et al. (2002). Differing recommendations may be due to a combination of greater variability in daily PA associated with a much younger sample and the smaller sample size of the former study. Notably, all

of these studies performed reliability analyses on minutes of PA and did not normalise outcome values to wear time, which takes into account the effects of variation in daily wear. Physical activity of maintenance HD patients is effectively clamped three days of the week due to a daily routine organised around therapy requirements and a compulsory period of inactivity. Reliability of accelerometer estimated PA and thus required wear time might therefore be different for dialysis days compared to non-dialysis days.

Hart et al. (2011c) recommended five days of accelerometer wear to achieve a desired reliability level of 0.80 for estimated sedentary behaviour defined as <50 cpm in a sample of older adults. Longer wear time requirements of one week and five to nine days are reported for middle-aged (Matthews et al. 2002) and young adults (Cook and Lambert 2008) respectively. Although similar uniaxial Actigraph accelometers were employed in all three studies, discrepant results may be the result of Matthews et al. (2002) and Cook and Lambert (2008) using an unorthodox cutpoint (<500 cpm) to determine sedentary behaviour. However, these results are consistent with the study of Ojiambo et al. (2011), which recommended eight days wear to estimate sedentary behaviour of children with the same level of reliability. It would appear sedentary behaviour is more variable on a day-to-day basis, and more susceptible to discretionary wear necessitating more monitoring days to estimate this behaviour with acceptable reliability. As with total PA, none of the cited studies calculated reliability for this sedentary behaviour on values adjusted for wear time.

Recommended monitor wear time for moderate to vigorous PA (MVPA) appears to reduce with advancing age which is attributed to observations that PA of this intensity is often planned, and less variable in older adults (Rowe et al. 2007). Five to nine days wear is recommended for Actigraph derived estimates of MVPA among junior school age children and adolescents (Trost et al. 2000). Cook and Lambert (2008) observed four to five days were required for acceptable reliability of MVPA in their sample of young rural and urban adults while three to four days were recommended for asymptomatic middle aged men and women (Matthews et al. 2002). In contrast, only two days of accelerometer wear were needed to reliably estimate MVPA of older adults (Hart et al. 2011c). Given the advanced average and weekly routine HD patients follow it is possible wear requirements for this population may fall somewhere between those of Hart et al. (2011c) and Matthews et al. (2002).

Several studies of people with stage 5 CKD have used activity counts obtained from triaxial accelerometers as a gross measure of habitual PA (table 1.3). Notably, only one PA reliability study was located that examined required accelerometer wear time using triaxial accelerometry in a sample of low-active young men (Coleman and Epstein 1998). The authors employed generalisability theory (signified by G*), a similar ANOVA based framework to the ICC in order to determine measurement reliability. The cited study indicated three to four days of monitor wear produced acceptable levels generalisability (G* >0.77 and G* >0.82 respectively) for triaxial activity counts obtained from a Tri-Trac-3D accelerometer. Earlier research by Gretebeck and Montoye (1992) using three Caltracs to simulate triaxial accelerometer output reported two days wear achieved a reliability level of 0.83 in a sample of 30 men (average age 36.9 years) using the Spearman Brown formula. Recommendations for uniaxial Actigraph accelerometers are not dissimilar with two to three days wear sufficient to provide a reliability level of at least 0.80 for healthy middle aged adults (Matthews et al. 2002; Cook and Lambert 2008) and older adults (Evenson et al. 2012). Large scale reliability studies undertaken with children, report wear time recommendations for uniaxial Actigraph accelerometers consistent with those for adults of two (Rich et al. 2013) or three days (Mattocks et al. 2008).

The only data pertaining to wear time recommendations for objectively estimated step counts come from reliability studies employing pedometers. Studies with monitoring protocols ranging from seven to 21 days (Tudor-Locke et al. 2005; Rowe et al. 2007 and Hart et al. 2011c respectively) and up to one year (Kang et al. 2009) suggest a minimum of two to six days wear for a reliability level of 0.80. As with accelerometer estimated PA outcomes the recommended monitoring period for older adults appears to be slightly less at two to four days (Rowe et al. 2007; Hart et al. 2011c) compared to three to six for middle-aged adults (Kang et al. 2009; Tudor-Locke et al. 2011c). Although step count is commonly used as a motivational outcome there is no literature regarding wear time requirements for accelerometer estimates of this index.

Taken together the reviewed studies indicate that three to five wear days are recommended to obtain reliable estimates of PA from accelerometers, but this may vary according to participant age, and variable of interest. In addition PA reliability studies have only recently begun to take into account variations in discretionary wear, which will have a bearing on recommendations (Hinkley et al. 2012). Notably,

PA reliability studies have almost exclusively relied on uniaxial Actigraph accelerometers and there is an absence of data regarding triaxial output from later models such as the GT3X. Furthermore there are no recommendations regarding other monitors employed in PA studies or novel devices such as the ActivPAL.

Deciding whether to retain or exclude participants without weekend monitor wear is another methodological consideration. There is little consensus regarding whether a weekend day is mandatory to reflect habitual PA of adults. Studies by Gretebeck and Montoye (1992) and more recently by Ojiambo et al. (2011) have recommended monitoring at least one weekend day. Weekend days are observed to have less time spent inactive compared to week days (Matthews et al. 2002; Parry and Straker 2013) with Sunday being a less active day than Saturday (Matthews et al. 2002). Time in MVPA is reported to be greater during the week compared to weekend days (Matthews et al. 2002). However, a recent study of older adults in residential care showed no significant difference in daily PA (Reid et al. 2013). There is general agreement purposeful inclusion of weekend PA does not improve reliability of outcome estimates from a population-based study of adults (McClain et al. 2010) and large cohort studies of children (Penpraze et al. 2006; Rich et al. 2013). The issue of purposeful inclusion of weekend PA is more complex for the HD population as therapy schedules differ between individuals. For example some are required to undergo therapy on a day regarded as a 'typical' weekend day. It may be more appropriate to define the two day reprieve from HD as the 'two day interdialytic period' rather than the weekend.

1.2.1.9 Defining a valid wear day

A guideline regarding the number of hours an accelerometer has to be worn per day is crucial to determine which days are ruled in and thus whether a participant's data meet the minimum requirement for acceptable reliability. For Actigraph monitors non-wear time determined by consecutive zero counts during data cleaning is an influential aspect of this guideline. Importantly, employing shorter periods of consecutive zero count minutes to identify monitor non-wear can reduce wear time (Evenson and Terry 2009) and the relative contribution of sedentary time in particular (Masse et al. 2005; Tudor-Locke et al. 2011d). It is argued that a proportion of what is categorised as non-wear time may in fact represent sedentary behaviour in less active, older or overweight populations (Masse et al. 2005; Tudor-Locke et al. 2011d; Toftager et al. 2013).

Sedentary time erroneously categorised as non-wear not only impacts the proportional contribution of monitored variables but also adversely affects the number of participants retained for analysis due to insufficient monitor wear (Masse et al. 2005; Toftager et al. 2013). There is general agreement that epochs of 90 to 180 consecutive zero count minutes provide similarly accurate and stable estimates of non-wear time for a range of adult populations (Troiano et al. 2008; Song et al. 2010; Oliver et al. 2011; Hutto et al. 2013). Determination of ActivPAL wear time for waking hour protocols can be more easily identified using the first and last transfers between lying/sitting and standing postures to define 'active' monitoring periods assuming the device is not removed.

A wear time criterion of ≥10 hours has been widely adopted to define a valid wear day (Trost et al. 2005; Troiano et al. 2008; Colley et al. 2010; Semanik et al. 2010; Tudor-Locke et al. 2011e). Interestingly, this standard was based on the research of Masse et al. (2005), which explored sample retention according to different non-wear algorithms and not computed reliability analyses. The 10 hour threshold was further enshrined in accelerometer practice with subsequent application to accelerometry data from the NHANES project, and inclusion into the SAS syntax accompanying the NHANES PA data (Tudor-Locke et al. 2012). In contrast, recent analysis of NHANES data suggested 13 hours as the required minimum wear per day to provide a valid measure of PA when using 14 hours wear as a reference (Herrmann et al. 2013). However, recommendations from the latter study did not take into account intra and inter-individual variation in monitor wear times. It is argued that accelerometer outcome variables should be normalised against total wear time in order to reduce measurement bias due to wear time variation (Chen et al. 2009; Hinkley et al. 2012).

An advantage of adopting the 10 hour wear threshold is that it allows direct comparison of findings with previous PA health research, but it is important to consider the unique characteristics of the HD population. These include high average age, high prevalence of multi-morbidity and debilitating symptoms. Therefore it may be impractical to expect every individual in this population to achieve the 10 hour benchmark. More recently, shorter wear time criteria of six to eight hours have been recommended for preadolescent participants (Steele et al. 2009; Jago et al. 2010; Ojiambo et al. 2011). Notably, a wear time threshold of eight hours is reported to provide similar levels of reliability to 10 and 12 hour thresholds when estimating habitual PA of populations that are typically sedentary (Chen et al.

2009; Miller et al. 2013). Another suggested wear day criterion is the 80/70 rule, which is derived using a study-specific ratio. A valid day is calculated as 80% of a 'standard day' with a standard day defined as the length of time 70% of the sample wore their monitor (Catellier et al. 2005; Masse et al. 2005).

1.2.1.10 Summary and research questions

Accelerometers are increasingly being employed to characterise behaviour of people with stage CKD, however, there appears to be low awareness of the importance of data quality assurance. Accelerometer wear time guidance exists for other populations but there are presently no recommendations regarding their implementation in stage 5 CKD. There is an urgent need for PA data reduction and processing guidelines to ensure accelerometer derived outcomes are reliable.

What is the minimum number of wear days required for ActivPAL and Actigraph accelerometers to obtain reliable estimates of habitual PA and sedentary behaviour of people receiving maintenance HD?

What is the recommended minimum number of accelerometer wear hours required to define a 'valid' wear day for people receiving maintenance HD?

How do different accelerometer wear criteria affect participant retention for final analysis in a sample of people undergoing maintenance HD?

1.2.1.11 Concordance of accelerometer estimates of activity behaviours

Interestingly, none of the CKD studies reviewed used accelerometers from the Actigraph family, despite their extensive use in large-scale epidemiological studies such as NHANES. In addition, much of the research regarding the deleterious effects of sedentary behaviour on metabolic health has been undertaken using Actigraphs. Only the Actiwatch 64, which was originally designed for sleep research has been employed to derive an estimate of sedentary behaviour of people with CKD. Importantly, characterising habitual PA and sedentary behaviour in stage 5 CKD using an Actigraph accelerometer would allow contextualisation with a large amount of existing research.

The GT3X (Actigraph Corp, Pensacola, Florida) is the latest Actigraph model, and can estimate activity from triaxial and uniaxial configurations. In contrast to uniaxial accelerometers, which only detect movement in the vertical axis, triaxial accelerometers measure accelerations in three orthogonal planes and should theoretically be more accurate. Output from the GT3X includes steps taken and energy expenditure (EE). In addition acceleration output can be categorised according to cutpoints to derive time spent at different levels of PA intensity that relate to health guidelines. However, monitoring only these outcomes may be inappropriate in the HD population, which is characterised by advanced average age, enforced sitting, and high prevalence of multi-morbidity and debilitating condition-related symptoms. Light intensity PA, represents the domain in which many routine ADLs are performed and constitutes around 20% of all daily activity (Levine et al. 2005). Moreover, accelerometer studies indicate all PA including light intensity is associated with longevity and physical function of maintenance HD patients (Johansen et al. 2001a; Kutsuna et al. 2010; Matsuzawa et al. 2012). An advantage of accelerometers like the Actigraph is that they are able to estimate behaviour at the lower end of the PA spectrum and differentiate this from sedentary time. Accumulating evidence linking sitting time with health outcomes (Owen et al. 2010, Thorp et al. 2011) and higher levels of sedentary behaviour in the HD population (Agarwal and Light 2011) provide a compelling argument for monitoring of this outcome.

As with PA categorisation, Actigraph estimates of sedentary time are determined by application of a specific cutpoint (<100 cpm) to activity data (Evenson et al. 2008). The ActivPAL (PAL Technologies Ltd, Glasgow) is a more recently developed

accelerometer which employs inclinometry to monitor sitting and standing behaviours and detect changes between these postures. Although Actigraphs have been widely adopted to characterise behaviour of populations and in studies exploring metabolic effects of sedentary time some doubts have surfaced regarding their ability to accurately estimate this outcome.

Concordance studies of Actigraph and ActivPAL estimates of sedentary behaviour report moderate to strong correlations (range r = 0.68 to 0.81) during free-living situations in pre-school age children (Martin et al. 2011) and adults (Clemes et al. 2012; Matthews et al. 2013). However, when level of agreement between these two devices is inspected the Actigraph is frequently found to estimate significantly higher amounts of sedentary time (mean systematic bias range: +44 to +132 mins/day) compared to ActivPAL (Hart et al. 2011a; Hart et al. 2011b; Clemes et al. 2012). The largest bias was observed with a 15 second data-sampling epoch (Hart et al. 2011a) suggesting epochs shorter than one minute exacerbate estimation discrepancies.

Matthews et al. (2013) and Ridgers et al. (2012) reported lower non-significant mean differences (+13.2 to +19.2 and +5.2 mins/day respectively), which may be attributed to use of later model Actigraphs (GT1M, GT3x) known to have reduced sensitivity to lower frequency movements. In addition, the monitoring period (390 minutes) in the latter study was comparatively short which likely reduced subsequent bias magnitude. In contrast Martin et al. (2011) found Actigraph estimated sedentary behaviour (expressed as a percentage of wear time) for pre-school children was lower than ActivPAL (-4.3% and -2.1% corrected/uncorrected estimates). Differing findings are likely due to a higher cutpoint (<1100 cpm) and inclusion of periods of 'quiet standing' in addition to lying/sitting time, which differs from the current consensus definition.

Actigraph cutpoint selection for determination of sedentary behaviour also appears to influence concordance with ActivPAL estimates. The widely adopted cutpoint of <100 cpm was originally calibrated with a sample of children aged five to eight years (Evenson et al. 2008). Validity of this threshold for adults has been evaluated more recently and there are indications that a <50 cpm cutpoint initially suggested by Crouter et al. (2006) may better reflect sedentary behaviour in free-living conditions. Application of this threshold is observed to produce lower mean systematic bias between ActivPAL and Actigraph monitors regardless of model

generation to a level, which is not statistically significant (Hart et al. 2011b; Clemes et al. 2012). Moreover Clemes et al. (2012) concluded a cutpoint of <50 cpm offered more favourable specificity and sensitivity for detecting sitting/lying compared to <100 cpm. In contrast Kozey-Keadle et al. (2011) found <150 cpm produced the lowest bias (compared to <50cpm and <100cpm) during a six hour direct observation protocol, but this result pertains only to later Actigraphs employing a low frequency filter extension.

Regardless of cutpoint choice, size and direction of measurement bias, there is general agreement that Actigraph and ActivPAL limits of agreement (LOA) are wide. Random error for a cutpoint of <100 cpm ranges from 143 to 570 mins/day around the mean bias (Hart et al. 2011b; Ridgers et al. 2012; Matthews et al. 2013) and 18.6% to 19.4% when normalised to monitor wear time (Martin et al. 2011). Moreover LOA observed with a lower Actigraph cutpoint of <50 cpm remain wide at over two hours either side of the mean bias (Hart et al. 2011b; Clemes et al. 2012). Notably, studies employing direct observation as a criterion measure during controlled and free living conditions indicate that classification of sedentary behaviour by ActivPAL is more precise compared to Actigraph regardless of cutpoint applied and manipulation of monitor sensitivity (Hart et al. 2011b; Kozey-Keadle et al. 2011; Lyden et al. 2012). Moreover, Actigraph output for standing still and washing dishes is below 100 cpm (Kozey et al. 2010), consequently this monitor may erroneously misclassify some routine light activities as sedentary behaviour. Taken together it would appear that ActivPAL provides a more precise proxy measure of sedentary behaviour compared to Actigraph.

An important research consideration of cited concordance studies is that few explicitly state whether wear epochs for ActivPAL and Actigraph were synchronised, which may have contributed to estimation discrepancies. Smaller bias between the devices was observed in studies where this aspect of data reduction was stated (Ridgers et al. 2012; Matthews et al. 2013). In addition, concordance studies for these monitors have been undertaken with younger, asymptomatic participants. In light of growing interest in the health consequences of sedentary behaviour and its particular relevance to stage 5 CKD, concordance of the Actigraph and ActivPAL monitors should be examined in a clinical population. Although several cutpoints exist to determine sedentary time from the Actigraph it would be prudent to evaluate concordance using the <100 cpm threshold to enable contextualisation of results with previous research.

Output from both ActivPAL and Actigraph accelerometers include activity counts and EE. While the Actigraph calculates EE from activity counts the ActivPAL estimates this outcome from an algorithm based on step rate. Harrington et al. (2011) found ActivPAL significantly underestimated EE compared to indirect calorimetry at all walking speeds (from 3.2 to 7.0 km/h) during a treadmill protocol in a sample of 62 young (15 - 25 years) women. The authors concluded a prediction equation based on activity counts as opposed to step rate would be more valid as the former was more strongly associated with indirect calorimetry ($r = 0.75$ vs 0.59, $p < 0.001$ respectively). However, this approach may not necessarily ameliorate estimation error as there is general agreement that Actigraph prediction equations based on activity counts underestimate EE irrespective of prediction equation employed (Welk et al. 2000; Leenders et al. 2001; Slootmaker et al. 2009; Albinali et al. 2010; Lyden et al. 2011). Taken together it appears both Actigraph and ActivPAL underestimate EE compared to criterion measures. No previous studies have evaluated concordance of EE estimates obtained from these devices.

Interestingly, although ActivPAL records activity counts the proprietary software does not currently convert this output into outcomes that are meaningful and interpretable such as PA intensity. Dowd et al. (2012) found activity count output from the two monitors correlated strongly ($rho = 0.96$, $p < 0.01$), however level of agreement has not been fully evaluated via Bland Altman analysis. Interestingly, the cited study indicated ActivPAL activity counts could be categorised, however the calibration was undertaken in a modest sample of 30 adolescent females limiting cutpoint generalisability. Cutpoints for categorising PA and EE already calibrated for the Actigraph could conceivably be generalised to the ActivPAL if agreement for this output was within acceptable limits.

Output from these monitors also includes the number of steps taken, a commonly employed motivational outcome. Notably, the stepcount capability of the Actigraphs has been employed to help characterise PA of the North American population in NHANES (Matthews et al. 2008). Studies employing direct observation concur that at moderate to brisk walking speeds ActivPAL and Actigraph estimated stepcounts do not differ significantly from each other (Harrington et al. 2011) or direct observation (Ryan et al. 2006; Sorti et al. 2008; Harrington 2011; Feito et al. 2012). However, there is general agreement from several criterion validity studies that later model Actigraphs (GT1M, GT3x) show a propensity to underestimate steps taken as gait decreases below 1.0 m/s (Sorti et al. 2008; Harrington 2011; Feito et al.

2012). Moreover studies employing 100-step treadmill and overground walking protocols agree magnitude of underestimation by Actigraph monitors increases to a startling 19% to 40% when ambulation speed drops under 0.80 m/s (Sorti et al. 2008; Feito et al. 2012). Although ActivPAL also underestimated steps at this speed the device still recorded 98% (± 3%) of directly observed steps (Feito et al. 2012). Similarly, Ryan et al. (2006) reported excellent criterion validity for ActivPAL at low gait speed with less than 1% error observed at 0.9 m/s. It is believed slower ambulation speeds affect accuracy of hip mounted accelerometers in a similar manner to pedometers by reducing the magnitude of vertical accelerations (Feito et al. 2012).

Notably ActivPAL step count accuracy evaluated by direct observation was lower for indoor compared to outdoor mobility (96.1% and 99.6% respectively) in a sample of 18 healthy adults (Busse et al. 2009). Indoor PA such as ADLs tend to be of lower intensity (Ainsworth et al. 2000) and more intermittent (Orendurff et al. 2008) with cadence that is unlikely to be continuous as in treadmill validation protocols. The consequences of gait speed on accuracy of step count estimation may be more profound in the HD population, which is characterised by slow gait (Painter et al. 2000) and advanced average age, which is also a determinant of walking speed (Bohannon 1997). Slow cadence appears to interact with stepcount estimates from both Actigraph and ActivPAL, however there are no studies evaluating concordance of this outcome in a clinical population like stage 5 CKD.

1.2.1.12 Summary and research question

Accelerometers such as the Actigraph and ActivPAL are increasingly being adopted in health research to obtain objective estimates of PA and sedentary behaviour. However, there is a paucity of information on concordance of similar outcomes obtained from these monitors in clinical populations. Research in this area is needed to support investigators and clinicians making an informed choice as to the most suitable device to assess a given behavioural outcome.

What is the level of agreement for shared physical activity outcomes obtained from Actigraph GT3x and ActivPAL accelerometers?

1.2.1.13 Questionnaire assessment of physical activity in stage 5 CKD

The majority (66%) of studies characterising PA of HD patients have employed self-report questionnaires exclusively, while a further 10% used a combination of subjective and objective methods. Up until 10 years ago self-reported exercise frequency was predominantly employed as a pragmatic PA metric. Subsequent studies with the exception of DOPPS (Tentori et al. 2010) have adopted questionnaires, which record different dimensions of habitual PA (mode, frequency, duration, intensity) to derive outcomes that translate to contemporary PA guidelines (table 1.4).

Table 1.4 Frequency of different PA questionnaires employed in stage 5 CKD.

Physical activity assessment tool	n	Studies		
Question/s on exercise habits	9	Painter et al. 2000 Painter et al. 2002 Stack et al. 2005	Allen & Gappelmaier 2001 Winkler et al. 2002 Tentori et al. 2010	Longenecker et al. 2002 O'Hare et al. 2003 Byrne & Russell 2011
Questions on habitual PA	1	Painter et al. 2011		
Human Activity Profile	13	Johansen et al. 2001b Bonner et al. 2009 **Comprehensive Dialysis Study** Johansen et al. 2010b; Kutner et al. 2010; Anand et al. 2011a; Anand et al. 2011b; Gordon et al. 2011; Johansen et al. 2013; Wasse et al. 2013; Anand et al. 2013	Johansen et al. 2003a Bonner et al. 2010	Wellard 2003
Baecke Activity questionnaire	2	Nielens et al. 2001	van de Ham et al. 2006	
Stanford 7 Day Recall	5	Johansen et al. 2000 Sakkas et al. 2004	Johansen et al. 2001b Sridharan et al. 2013	Nielens et al. 2001
Physical Activity Scale for the Elderly	3	Johansen et al. 2001b	Baria et al. 2011	Rosas et al. 2012
International Physical Activity Questionnaire	3	Li et al. 2010	Stringuetta-Belik et al. 2011	Leng et al. 2012
Global Physical Activity Questionnaire	1	Wong et al. 2011		
EPIC-Norfolk activity Questionnaire	1	Brenner & Brohart 2008		
KDQOL-SF 'activity questions'	1	Hicks et al. 2004		

Of the eight different questionnaires employed in stage 5 CKD research the Human Activity Profile (HAP) is the most frequently cited instrument due to publications arising from the Comprehensive Dialysis Study (table 1.4). However, responses in the HAP are reduced to a linear score derived from the number of different activities able to be performed while other PA dimensions are not quantified. Although the HAP is strongly correlated with accelerometer estimated PA (Johansen et al.

2001b) it is not an appropriate surrogate measure of habitual activity and is more indicative of functional status.

Other questionnaires such as the Baecke Activity Questionnaire (Baecke et al. 1982) and Physical Activity Scale for the Elderly (PASE) derive a linear score from responses relating to PA frequency, duration and intensity based on predefined descriptors and epochs. However, outcomes obtained from these questionnaires do not readily translate to PA guidelines. Of the questionnaires quantifying PA according to its different dimensions the Stanford 7 Day Recall (7DR) (Sallis et al. 1985) has been used the most frequently, while the international physical activity questionnaire (IPAQ) has been employed more recently (Li et al. 2010; Stringuetta-Belik et al. 2011; Leng et al. 2012). Although it is an older questionnaire there are indications the 7DR may be a better instrument for estimating PA associated with a health protective effect in stage 5 CKD. Higher systematic and random error relative to accelerometry is reported for the IPAQ compared to the 7DR in a cohort of women with breast cancer (Johnson-Kozlow et al. 2006). Moreover, the same study observed superior sensitivity and specificity for the 7DR in classifying individuals according to PA guidelines.

Despite the number of studies employing PA questionnaires in CKD research, there is a paucity of studies evaluating concordance of these instruments with objective measures, which are increasingly being used. To date the 7DR is the only questionnaire assessing different dimensions of habitual PA that has been evaluated for concordance with an objective measure in the HD population. Johansen et al. (2001b) found a moderate association between 7DR derived total EE (kcals/kg/day) and triaxial (Tri-Trac R3D) activity counts/day ($r = 0.59$, $p = 0.0005$) in a sample of 31 HD participants. However, activity counts are not readily interpretable or meaningful as a PA outcome making these findings of limited value in determining whether 7DR outcomes may be used interchangeably with objective measures or whether data may be directly compared or pooled.

Importantly, large epidemiological studies undertaken in the general population indicate a mismatch between what people report they do and their PA level as estimated by accelerometers. Participants in NHANES reporting >150 minutes of MVPA/week accumulated an average of just 57 minutes/week according to accelerometry (Schuna et al. 2013). The Canadian Health Measures Study found that although over half of Canadian adults reported being at least ‘moderately

active', accelerometer estimates indicated just 15% met PA guidelines (Colley et al. 2011). Results from the Health Survey for England indicate an even wider disparity in the UK (Townsend et al. 2012). There is general agreement from systematic reviews that the relationship between self-reported and objectively estimated PA outcomes is weak to moderate (van Poppel et al. 2010; Helmerhorst et al. 2012) averaging a relatively modest r = 0.37 overall (Prince et al. 2008). Moreover few PA questionnaires demonstrate acceptable levels of reliability across different age groups, a property which is often poorly assessed (Helmerhorst et al. 2012; van Poppel et al. 2010).

The majority of studies evaluating concordance of 7DR-derived PA estimates with accelerometry have observed weak to moderate associations for shared estimated outcomes (table 1.5). However, correlational analysis only tests strength of association between two assessment techniques and does not evaluate systematic bias or level of agreement (Bland and Altman 1986), and thus whether instruments may be used interchangeably. On the whole, level of agreement between the 7DR and accelerometer estimated PA outcomes is infrequently examined. Three studies from which level of agreement results could be extracted indicated a systematic bias with 7DR MVPA estimates higher than those derived via accelerometry (Timperio et al. 2003; Johnson-Koslow et al. 2006; Soundy et al. 2007). Although the bias observed by Johnson-Koslow et al. (2006) was not statistically significant, all cited studies demonstrated wide limits of agreement (LOA) and thus a large amount of random error/biological variation. Moreover, amount of random error observed for average daily MVPA by Timperio et al. (2003) was greater than weekly PA recommendations. In addition, correlations between the 7DR and accelerometry were not only lower for women (Richardson et al. 2000; Timperio et al. 2003) as observed in the wider PA literature (Prince et al. 2008) but random error was also comparatively greater (Timperio et al. 2003).

Moderate to strong associations are observed for EE outcomes derived from 7DR and objective measures (table 1.6). Stronger correlations are generally found for total EE, which may be due to a data smoothing effect of whole day estimates as associations between PA related EE are generally lower (Matthews and Freedson 1995; Richardson et al. 2001). Although correlations for total EE are stronger, current consensus guidelines emphasise the importance of EE accumulated during time in MVPA for a health-protective effect.

Table 1.5 Concordance of 7DR questionnaire MVPA outcomes with objective measures.

Study	Sample	Age	Objective measure	Correlation	Sig difference	Bland and Altman analysis
Garfield et al. 2012	COPD n = 43	68.0 ± 9.0	Sensewear Armband	MVPA r = 0.54 (p < 0.001)	Not tested	Not done
Soundy et al. 2007	Severe mental illness n = 14	52.9 ± 9.0	TriTrac-R3D	MVPA No correlation p value (not stated)	Not tested	7DR moderate PA mean bias: +16.9 mins/day (calculated LOA -87.5 to 121.3 mins/day) 7DR vigorous PA mean bias -10.4 mins/day (calculated LOA-58.0 to +37.3 mins/day.
Johnson-Kozlow et al. 2006	Women with breast cancer n = 159	56.6 SD not stated	Actigraph (CSA 7164)	MVPA mins rho = 0.73 (p <0.001)	No sig' difference (p value not stated)	Mean bias 7DR MVPA +22 mins/week (LOA +226 to -182 minutes/week.
Hayden-Wade et al. 2003	Asymptomatic adults n = 69	33.8 ± 11.2	TriTrac-R3D	MVPA mins r = 0.41 Moderate PA r = 0.34 Hard PA r = 0.43 V. Hard PA r = 0.71 (p values not stated)	Not tested	7DR estimates of all PA intensities higher but LOA and bias not stated.
Timperio et al. 2003	Asymptomatic adults n = 59	39.0 ± 15.0	Actigraph (CSA 7164)	Men MVPA mins rho = 0.29 (p < 0.05) Women MVPA mins rho = 0.25, (p < 0.05)	Yes (p < 0.001) Z value not stated	Men 7DR MVPA mins: +35.3 ± 71.2 mins/day (calculated LOA: -104.3 to +174.9 mins/day) Women 7DR MVPA mins: +69.0 ± 127.8 mins/day (calculated LOA: -122.7 to +319.5.
Leenders et al. 2000	Asymptomatic women n = 11	26.0 ± 6.0	Actigraph (CSA 7164)	MVPA mins not tested	No sig' difference (p value not stated)	Not done
Ainsworth et al. 2000	Asymptomatic adults n = 83	46.2 ± 15.4	Actigraph (CSA 7164)	Moderate PA rho = 0.26, Hard PA rho = 0.32	Not tested	7DR estimates of all PA intensities higher but LOA and bias not stated.

Table 1.6 Concordance of 7DR questionnaire energy expenditure outcomes with objective measures.

Study	Sample	Age	Objective measure	Correlation	Sig' difference	Bland and Altman analysis
Garfield et al. 2012	COPD n = 43	68.0 ± 9.0	Sensewear Armband (Total kcals/day)	r = 0.83 (p < 0.001)	Not tested	Mean bias 7DR total EE: +410 kcals/day. (LOA -262 to 1082 kcals/day).
Soundy et al. 2007	Severe mental illness n = 14	52.9 ± 9.0	TriTrac-R3D (Total kcals/day)	r = 0.43 (p = not stated)	Not tested	Mean bias 7DR total EE: +606.5 kcals/day (SD and LOA not stated).
Mahabir et al. 2006	Post-menopausal women n = 65	59.9 ± 7.5	Doubly Labelled Water (Total kcals/day)	rho = 0.47 (p < 0.05)	Yes (p < 0.05)	Mean bias 7DR total EE: +732 kcals/day (16%) (LOA +2860 to 1394).
Richardson et al. 2001	Asymptomatic adults n = 77	37.5 ± 10	Caltrac (METmins/day) Total PA Very Hard PA Moderate PA	 Men rho = 0.60 (p < 0.01) Women rho =0.36 (p < 0.01) Men rho = 0.49 (p < 0.05) Women rho = 0.57 (p < 0.01) Men rho = 0.52 (p < 0.01) Women rho = 0.17 (p > 0.05)	Not tested	Not evaluated
Allor & Pivarnik 2001	Adolescent females n = 46	12.0 ± 0.6	Caltrac (kcals/hr) Heart rate (kcals/hr)	r = 0.76 (p < 0.01) r = 0.50 (*p* < 0.01)	Yes (p < 0.01)	7DR kcals/hr 146 ± 43 vs Caltrac 100 ± 26 vs Heart rate 166 ± 41. LOA not stated.
Leenders et al. 2001	Asymptomatic women n = 30	25.8 ± 1.6	Doubly Labelled Water (PA kcals/day)	Not stated (between 0.42 and 0.55, p < 0.05)	No (p > 0.05)	7DR PA mean bias: not stated (LOA -633 to +280 kcals/day).
Bonnefoy et al. 2001	Asymptomatic older adults n = 19	73.4 ± 4.1	Doubly Labelled Water (Total kcals/day)	rho = 0.51 (p < 0.05)	No (p = 0.09)	7DR total EE bias: +276 kcal/d or 10.8% (LOA -1075 to +1625 kcals/day)
McDermott et al. 2000	Peripheral arterial disease & controls n = 41	67.2 ± 7.0 66.1 ± 5.4	Caltrac (kcals/week) v 7DR MET hours	rho = 0.60 (p < 0.001)	Not tested	Not evaluated
Leenders et al. 2000	Asymptomatic women n = 11	26.0 ± 6.0	Actigraph CSA 7164 (PA kcals/kg/day)	r = 0.82 (p < 0.001)	Yes (p < 0.05)	7DR PA EE: 9.7 kcal/kg/day vs Actigraph 5.4 7 kcal/kg/day. LOA not stated.
Matthews & Freedson 1995	Asymptomatic adults n = 25	26.7	TriTrac R-3D (kcals/day)	Total r = 0.77 (p < 0.001) MVPA r = 0.51 (p < 0.01)	Yes (p < 0.001) Not tested	7DR total EE bias: +310.3 kcals/day LOA not stated
Miller et al. 1994	Physiotherapists n = 33	28.0 ± 5.5	Caltrac	Total EE r = 0.79 (p < 0.01)	Not tested	Not evaluated.

Several studies agree 7DR estimated EE is significantly higher than values obtained from three different accelerometers (Miller et al. 1994; Matthews and Freedson et al. 1995; Leenders et al. 2000; Allor and Pivarnik 2001). However, heterogeneity of accelerometers and inconsistent standardisation of EE outcome hamper the synthesis of results to ascertain overall degree of bias. In contrast only one of three criterion validity studies employing doubly labelled water (DLW) found the 7DR significantly overestimated EE (Mahabir et al. 2006). Nevertheless, wide LOA were observed by all studies (table 1.6) indicating that utility of the 7DR as a proxy measure of EE at an individual level was limited. Moreover, Leenders et al. (2001) found differences in activity derived EE were related to PA level (overestimation with lower PA, underestimation with higher PA). Agreement analysis with accelerometry derived EE outcomes is scant with only bias level data reported (Matthews and Freedson 1995) or Bland-Altman plot LOA not stated (Allor and Pivarnik 2001).

Overall concordance studies show broad agreement between the 7DR and objective measures, but indicate questionnaire utility is limited at an individual level. Modest concordance between 7DR and accelerometry is largely attributed to reporting error, which increases with greater contribution of lower intensity PA to the total amount of habitual activity (Durante and Ainsworth 1996; Duncan et al. 2001). In contrast self-reported vigorous PA is more strongly associated with accelerometery, due to being well defined, often scheduled and thus easier to recall (Durante and Ainsworth 1996; Richardson et al. 2001; Timperio et al. 2003). Nonetheless, Buchowski et al. 1999 observed PA above 4.5 METs was oversestimated during two days of room calorimetry monitored living. Differential effect of activity intensity on PA recall may exacerbate questionnaire error in stage 5 CKD, which is characterized by high prevalence of difficulty with moderate to vigorous PA (Stack and Murthy 2008).

Limitations of accelerometry may also contribute to modest concordance with 7DR outcomes. Accelerometers are unable to detect increased work from gradient change during walking (Melanson and Freedson 1995), cycling, and load bearing activities (Westerterp 1999; Welk 2002) and cannot be worn swimming. In addition, they rely on calibrated cutpoints to categorise PA and calculate EE. Cutpoints and EE prediction equations are developed from calibration studies employing indirect calorimetry during treadmill walking or ADL protocols (Freedson et al. 1998; Swartz et al. 2000; Crouter et al. 2006). However, aerobic fitness, biomechanical efficiency, and resting metabolic rate decline with advancing age (Fitzgerald et al. 1997, Byrne et al. 2005; Kozey et al. 2010) and sedentary behaviour (Duncan et al. 2001).

Consequently, an activity at a given 'absolute intensity' will require a greater 'relative' percentage of VO_{2max} in older and/or more sedentary individuals.

Five previous studies have evaluated concordance of similar 7DR and Actigraph outcomes (tables 1.5 and 1.6). The prediction equation and cutpoints employed by the Actigraph software to calculate EE and categorise PA were developed from a calibration study employing a treadmill protocol of 'slow walking', 'brisk walking' and 'jogging' (Freedson et al. 1998). Notably, the 'slow walking' component was a speed of 4.8 km/hr (1.3 m/s), which is still higher than the average gait speed of most HD patients. Recent research supports the validity of the widely used Freedson et al. (1998) cutpoints for 'absolute' measures of MVPA in 20 to 69 year olds (Miller et al. 2010). However, the same study suggested application in older adults may be limited as MVPA cutpoints for the Actigraph were significantly different when expressed relative to an individual's maximum aerobic power and age. Notably, Timperio et al. (2003) observed stronger associations between 7DR and accelerometer estimates of moderate PA when the threshold was lowered from 3.0 METs (≥1952 cpm) to 2.5 METs (≥1334 cpm) for overweight men (rho = 0.39 and 0.46 respectively, $p < 0.01$) and women (rho = 0.21 to 0.40 respectively, $p < 0.05$).

There is general agreement that accelerometry underestimates EE during controlled walking and ADL protocols as well as free living situations when compared to direct calorimetry and doubly labelled water respectively (Welk et al. 2000; Slootmaker et al. 2009; Albinali et al. 2010). Moreover, underestimation occurs whether the EE equation is based on single linear (Freedson et al. 1998; Hendelman et al. 2000; Swartz et al. 2000) or dual regression models (Crouter et al. 2006). It is also suggested accuracy of accelerometry derived PA outcomes may depend on type of typical activity and population the prediction equations were originally calibrated for.

1.2.1.14 Summary and research question

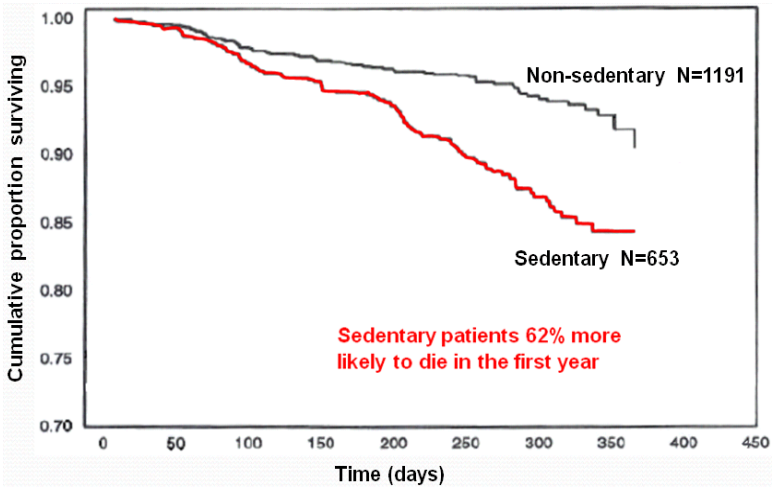
Concordance studies for the 7DR in the general literature are predominantly drawn from samples of younger participants limiting generalisability to the stage 5 CKD population. Given the number of CKD studies with 7DR data it would be advantageous to evaluate concordance of this instrument with an objective measure to facilitate data pooling and synthesis of results.

What is the level of agreement between subjective and objectively estimated PA outcomes in stage 5 CKD?

1.2.1.15 Physical activity and mortality in stage 5 CKD.

It is important to address issues regarding PA surveillance in the stage 5 CKD population as large-scale epidemiological studies demonstrate PA level is inversely related to CV and all-cause mortality of people with stage 5 CKD (table 1.7) as it is in the general population (Blair et al. 2001; Lee and Skerrett 2001; Warburton et al. 2006; Beddhu et al. 2009). Sedentary incident HD patients in the Dialysis Morbidity and Mortality Study (DMMS) were 62% more likely to die during their first year (figure 1.6) compared to non-sedentary individuals (O'Hare et al. 2003).

Figure 1.6 Sedentary behaviour and first year mortality. (O'Hare et al. 2003, p. 451).



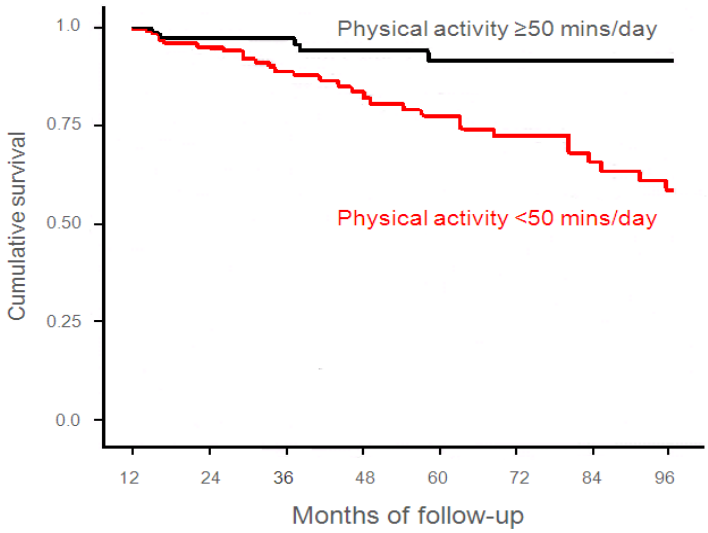
Importantly, exercise frequency was independently associated with survival in both the DMMS and larger Dialysis Outcomes and Practice Patterns Study (DOPPS) (Tentori et al. 2010). Illustratively, mortality risk for dialysis patients who exercised more than twice a week was 26 - 31% lower than sedentary individuals (Stack et al. 2005; Tentori et al. 2010), comparable to observations in the general population (Nocon et al. 2008). Not only did survival improve progressively with exercise frequency, mortality risk declined by 9% for every 10% increase in regular exercisers at a renal unit (Tentori et al. 2010). Self-reported PA is also independently predictive of all cause and CV mortality among kidney transplant recipients (Rosas et al. 2012 and Zelle et al. 2011). Although a single question regarding exercise frequency has been shown to be predictive of survival, this behavioural metric excludes other beneficial habitual PA. Exercise forms a sub-domain of PA, which is defined as: "any bodily movement produced by skeletal muscles that results in energy expenditure" (Caspersen et al. 1985, p. 126).

Table 1.7 Epidemiological studies of physical activity and survival in stage 5 CKD.

Study	Sample (n)	M/F %	Age	PA measure	Design	Outcome
Johansen et al. 2013 Comprehensive Dialysis Study	Incident HD & PD, (n = 1554)	55/45	59.8 ± 14.2	Human activity profile	Multi-centre, prospective study. Median follow up 2.6 years (2.2 - 3.1).	Increased mortality risk per 10 point reduction of HAP adjusted activity score HR = 1.30 (CI: 1.23 - 1.39).
Matsuzawa et al. 2012	Prevalent HD (n = 202)	48/52	64 (57 - 42)	Lifecorder uniaxial accelerometer	Prospective single centre. Mean follow up 45 months (range 2 - 84).	≥ 50 mins of total PA per day significantly associated with better survival (Log rank p = 0.001). Adjusted mortality risk per 10 minute increase of total daily PA: HR = 0.78 (CI: 0.66 - 0.92, p = 0.002).
Rosas et al. 2012	Transplant recipients, (n = 507)	61/39	51.4 ± 13.1 (inactive) 47.3 ± 12.7 (moderate) 44.8 ± 11.6 (active)	Physical Activity Scale for the Elderly	Multi-centre, prospective study. Median follow up 8.4 yrs (7.2 - 9.6).	All cause mortality according to tertiles of increasing PA: **inactive 36.3%**; moderately active **23.3%**; active **16.3%** (p = 0.01). PA level inversely associated with all cause mortality. Most active vs inactive tertile: HR = 0.52 (CI: 0.31 - 0.87; p = 0.01).
Zelle et al. 2011	Transplant recipients > 1 yr, (n = 540)	54/46	51 ± 12	Tecumseh Occupational Activity Questionnaire, Minnesota Leisure Time Physical Activity Questionnaire	Single-centre prospective study with retrospective 12 month PA. Median follow up 5.3 yrs (4.7 - 5.7).	All cause mortality according to tertiles of PA: **inactive 24.4%,** moderately active **15.0%**, active **5.6%** (p = 0.001). CV mortality: **11.7%, 7.1%**, **1.7%** (p < 0.001) CV mortality risk with increasing PA: HR 0.62 (CI: 0.45 - 0.86, p = 0.004) adjusted for age, gender, CVD history, Framingham risk score, BP, waist size, smoking.
Tentori et al. 2010 Dialysis Outcomes & Practice Patterns Study	Prevalent HD (n = 20912)	Not stated	Not stated	Single question on exercise frequency	Multi-centre prospective study. Mean follow up 3.6 ± 1.9 yrs.	Exercise frequency and survival advantage (adjusted): ≥ 1x/week RR 0.73 (CI: 0.69 - 0.78, p < 0.0001) 2 - 3x/wk RR 0.72 (CI:0.66 - 0.79, p < 0.0001) 4 - 5x/wk RR 0.73 (CI:0.62 - 0.86, p ≤ 0.0002) 6 - 7x/wk RR 0.69 (CI:0.63 - 0.76, p < 0.0001) 10% increase in facility regular exercisers associated with 9% lower mortality risk (CI 0.89 - 0.94, p < 0.0001).
Stack et al. 2005 Dialysis Mortality & Morbidity Study	Incident HD & PD (n = 2064)	54/46	58.0 ± 16	Single question on exercise frequency	Multi-centre prospective study. Mean follow up 3.6 ± 1.9 yrs.	Exercise frequency and survival advantage (adjusted): 2 - 3x/wk RR 0.74 (CI: 0.58 - 0.95, p < 0.05) 4 - 5x/wk RR 0.70 (CI: 0.47 - 1.04, p = 0.07) Daily RR 1.06 (CI: 0.86 to 1.30, p > 0.05).
O'Hare et al. 2003 Dialysis Mortality & Morbidity Study	Incident HD & PD (n = 2264)	54/46	58.0 ± 16	Single question on exercise frequency	One year follow-up	First year mortality - Sedentary 11% vs non-sedentary 5%. Sedentary mortality risk HR 1.62 CI:1.16 - 2.27 (p = 0.005).

Matsuzawa et al. (2012) found that 50 mins/day of all PA (>1.8 METs) estimated via accelerometry was independently associated with lower all-cause mortality over four years (figure 1.7). Moreover, each 10 minute increment of accumulated PA equated to a 22% reduction in all-cause mortality. Interestingly, this study did not differentiate between PA attributed to daily ADLs and PA associated with a cardio-protective effect. Nonetheless, the results are consistent with evidence that as little as 10 - 15 minutes PA is also beneficial to health outcomes (Samitz et al. 2011; Sattlmair et al. 2011; Wen et al. 2011).

Figure 1.7 Objectively estimated PA and survival of HD patients (Matsuzawa et al. 2012, p. 4).



1.2.1.16 Physical activity and intermediate health outcomes in stage 5 CKD

Deranged bone metabolism, and subsequent bone dystrophy is one of the sequelae of CKD and highly prevalent among HD patients (Ambrus et al. 2010). Secondary hyperparathyroidism is believed to be an important mediating factor in bone demineralisation (Taal et al. 1999) but PA level may also play a role. Pedometry derived daily energy expenditure (EE) is independently associated with dual energy x-ray absorptiometry measured bone mineral density of women receiving maintenance HD (Ota et al. 1997). As well as having clear implications for higher fracture risk among HD patients (Chang et al. 2013), bone demineralisation has been linked to CV morbidity and mortality in the general population (Farhat and Cauley 2008).

Decreased concentration of high-density lipoprotein (HDL) often associated with elevated levels of harmful triglycerides, is a common feature of uraemia (Imamura et al. 2012). Average daily pedometer steps of HD patients is independently associated with an HDL subfraction and significantly associated with apolipoprotein (Apo) A-I (Masuda et al. 2009). Importantly the latter is responsible for modulating lipid metabolism and predictive of myocardial infarction (McQueen et al. 2008). In addition, moderate inverse associations with pedometry have been observed for serum cholesterol and triglyceride levels of HD patients (Nowicki et al. 2010).

Systemic inflammation is also implicated in CVD genesis, however triaxial accelerometry PA studies either observe no correlation with pro-inflammatory cytokines (Hung et al. 2002) or report an inverse association without detailing the strength and significance of observed relationships (Johansen et al. 2003a). Mafra et al. (2011) found moderate to strong associations between C-reactive protein (CRP) and total EE as well as steps estimated by the Sensewear Armband. However, other studies employing the same device observed either only a trend (Avesani et al. 2012) or no association with any PA parameter (Baria et al. 2011; Cupisti et al. 2011). Pedometer studies also report contrasting results with high sensitivity CRP (Zamojska et al. 2006; Nowicki et al. 2010). Inconsistent findings are possibly due to some studies being statistically underpowered (<30 participants), high inter-individual differences in inflammatory markers and condition variability.

Increased visceral adiposity is a putative CV risk factor and indices of objectively estimated PA are inversely associated with BMI in stage 5 CKD (Mafra et al. 2011; Avesani et al. 2012), which is consistent with findings in the general population. Moreover, serum concentration of Leptin the satiety hormone produced by adipose tissue is inversely associated with objectively estimated PA of HD patients (Johansen et al. 2003a). It is speculated studies reporting no relationship between objectively estimated PA and BMI (Johansen et al. 2000) or reverse epidemiology (Zamojska et al. 2006; Cupisti et al. 2011) may in fact reflect better nutritional status of participants. A growing body of literature (table 1.8) indicates PA is linked to traditional CV risk factors and some of the criteria for metabolic syndrome (dyslipidaemia; hypertriglyceridaemia; central obesity; glucose intolerance; hypertension), which affects around two thirds of HD patients (Young et al. 2007; Shahrokh et al. 2012; Tu et al. 2012). Overall, stronger correlations with markers of health status are observed for objectively estimated PA compared to self-report which is consistent with findings from NHANES data (Atienza et al. 2011).

Table 1.8 Physical activity and clinical indices of health status in stage 5 CKD.

Study	Sample (n)	M/F %	Age	PA measure	Associations with anthropometric and physiological variables
Avesani et al. 2012	Prevalent HD (n = 134)	64/36	54.9 ± 15.9	Sensewear Pro2 Armband	**Age:** total EE r = 0.51; PA EE r = 0.34; steps r = 0.49; PA level r = 0.27 ($p < 0.001$). **BMI:** total EE r = -0.20; steps r = -0.21; PA level r = -0.28 ($p < 0.001$); PA EE r = 0.20 ($p < 0.05$) . **Serum creatinine:** total EE r = 0.37; steps r = 0.30 ($p < 0.001$). **CRP:** steps r = -0.16 ($p = 0.06$). Age and diabetic status main determinants of steps/day ($r^2 = 0.30$). Diabetes and BMI determinants of PA level ($r^2 = 0.12$).
Stringuetta-Belik et al. 2012	Prevalent HD (n = 102)	55/45	58.7 ± 15.1	IPAQ	Risk of cognitive dysfunction (Mini Mental State Examination) lowest for active compared to sedentary: RR 0.06, (CI 0.01 - 0.76, $p = 0.03$).
Wong et al. 2011	Prevalent HD (n = 70)	59/41	57.0 ± 12.5	Global physical activity questionnaire	**Serum creatinine:** r = 0.34 ($p = 0.004$), **education level:** r = 0.36 ($p = 0.002$), **income:** r = 0.33 ($p = 0.006$), **potassium knowledge:** r = 0.26 ($p = 0.029$)
Cupisti et al. 2011	Prevalent HD (n = 50) Controls (n = 33)	64/36	59.0 ± 13.0	Sensewear Pro2 Armband	Total EE: **BMI** r = 0.51 ($p < 0.001$), **phase angle** r = 0.40 ($p < 0.01$), **serum phosphate** r = 0.49 ($p < 0.001$) **albumin** r = 0.41 ($p < 0.01$). Mean daily METs: **normalized energy intake** r = 0.47 ($p < 0.001$); **protein intake** r = 0.33 ($p < 0.05$); **phase angle** r = 0.38 ($p < 0.01$). Minutes of PA >3METs: **phase angle** r = 0.36 ($p < 0.01$); **body cell mass index** r = 0.41 ($p < 0.01$); **normalized energy intake** r = 0.51 ($p <0.001$); **dietary protein intake** r = 0.37 ($p < 0.01$). No relationship between PA parameters and CRP,Kt/V, Hb or Hct.
Baria et al. 2011	Prevalent HD (n = 32) Sed'controls (n = 22).	63/37	46.3 ± 12.2	Sensewear Pro2 Armband	Activity related EE associated with: **lean body mass%** r = 0.42 ($p = 0.02$), **body cell mass %** r = 0.35 ($p =0.047$). Not associated with CRP, Hb, Hct, creatinine, albumin.
Mafra et al. 2011	Prevalent HD (n = 24) Controls (n = 18)	75/25	67.0 ± 14.7 62.3 ± 15.3	Sensewear Pro2 Armband	Total EE and **CRP** r = -0.70 ($p = 0.0001$); step counts and **CRP** r = -0.62 ($p = 0.001$).
Gordon et al. 2011	Prevalent HD (n = 58)	70/30	55 ± 13	TriTrac-R3D triaxial accelerometer n = 26 Human activity profile (HAP)	**Post-dialysis fatigue index score** and activity counts r = -0.45 ($p = 0.02$); HAP adjusted activity score (r = -0.32, $p = 0.02$) Activity counts largest contributor to post dialysis fatigue after adjustment for Kt/V and dialysis vintage $r^2 = 0.40$ ($p = 0.009$). Self-reported PA not retained in multiple regression model.
Li et al. 2010	Prevalent HD (n = 187)	51/49	59.0 (IQ not stated)	International Physical Activity Questionnaire	Activity related EE associated with: serum albumin concentration (r = 0.16, $p < 0.05$), physical function (r = 0.47, $p < 0.001$) and SF-36 physical component summary scores (r = 0.32, $p < 0.001$).

Study	Sample (n)	M/F %	Age	PA measure	Associations with anthropometric and physiological variables
Bonner et al. 2010	Prevalent HD, PD, Predialysis, KT (n = 112)	60/40	55.0 (SD not stated)	Human Activity Profile	**Fatigue severity scale** r = 0.49 (p < 0.01).
Nowicki et al. 2010	Prevalent HD (n = 33)	52/48	58.3 ± 10.1	Step count Pedometer	**Cholesterol** r = 0.35 (p = 0.04); **triglycerides** r = 0.45 (p = 0.008); **albumin** r = 0.43 (p = 0.012); **haemoglobin** r = 0.37 (p = 0.033); **haematocrit** r = 0.36 (p = 0.04); **C-reactive protein** r = -0.39 (p = 0.023).
Kutsuna et al. 2010	Prevalent HD (n = 153)	42/58	64.0 ± 11.0	Lifecorder uniaxial accelerometer	50 minutes of all PA per day (> 1.8 METs) required to prevent deterioration in normal and maximum walking speed. Area under curve = 0.78.
Masuda et al. 2009	Prevalent HD (n = 35) Prevalent PD (n = 26)	69/31	58.3 ± 14.7 47.5 ± 14.2	Omron pedometer.	Steps/day independently associated with **HDL2-C** r = 0.38 (p < 0.05) and **apolipoprotein (Apo) A-I** r = 0.37 (p < 0.01). Trends for **HDLC** r = 0.38 (p = 0.051) **HDL 3 -C** r = 0.32 (p = 0.062) Highest tertile of steps/day (4,060–8,410) had significantly higher HDL 2-C and Apo A-I compared to lowest (50–2,530 steps/day).
Zamojska et al. 2006	Prevalent HD (n = 60) Controls (n = 16)	45/55 36/64	60.0 ± 13.0 56.0 ± 6.0	Pedometer (Oregon Scientific)	Step count and **Hb** r = 0.42 p = 0.001) **Hct** (r = 0.46, p = 0.001); **serum albumin** r = 0.32 p < 0.01); **phase angle** r = 0.46 p = 0.002).
Majchrzak et al. 2005	Prevalent HD (n = 20)	50/50	50.1 ± 9.9	Hip mounted RT-3 triaxial accelerometer	Non-dialysis activity counts and **prealbumin** (r = 0.52 p = **.019)**, Trends for **cholesterol** r = -0.43 (p = 0 .058), **CRP** r = -0.41 (p = 0.073).
Johansen et al. 2003a	Incident HD (n = 54)	67/33	51.7 ± 17	TriTrac-R3D triaxial accelerometer. Human activity profile 4 time points over 12 months	Activity counts and **serum IL-1β** (correlation and p value not stated) Activity counts declined by 17000 with each log increase in leptin concentration (p = 0.0015).
Hung et al. 2002	Prevalent HD (n = 47)	66/34	50.3 ± 16.7	TriTrac-R3D triaxial accelerometer	Age adjusted associations with **protein intake** r^2=0.42 (p = 0.004); **caloric intake** r^2 = 0.34 (p = 0.03). Inflammation not associated with PA.
Johansen et al. 2000	Prevalent HD (n = 34) Sed' controls (n = 80).	65/35	51.5 ± 3.0	TriTrac-R3D triaxial accelerometer	Activity counts and **albumin** r = 0.57 (p = 0.003); **phase angle** r = 0.40 (p = 0.02); **creatinine** r=0.37 (p = 0.03).
Ota et al. 1997	Prevalent HD patients n = 41	0/100	61.0 ± 16.0	Pedometer calorie counter (Suzuken)	Energy expenditure independently associated with **total bone mineral density measured** by DEXA (p < 0.0001) after adjustment for age, dry body weight, HD vintage, serum protein.

KT = Kidney transplant recipients

While data regarding the relationship between PA and metabolic syndrome among maintenance HD patients is scant, it likely mirrors the positive relationship observed for kidney transplant (KT) recipients (Zelle et al. 2011). Metabolic syndrome is suggested to be a pre-disease state that not only foreshadows CVD and predicts CV events in stage 5 CKD (Wu et al. 2011) but also increases the risk of new onset diabetes almost threefold (Bonet et al. 2013). Worryingly, not only were HD patients with diabetes in the study of Majchrzak et al. (2005) significantly less active than non-diabetics, the disparity widened from 46% to 60% on dialysis days and non-dialysis days respectively.

There is general agreement that indices of objectively estimated PA obtained via accelerometry are associated with biochemical and anthropometric indicators of nutritional status (table 1.8). Average daily stepcount, MVPA, daily EE and activity counts are moderately correlated with serum albumin, phase angle and body cell mass index (Johansen et al. 2000; Zamojska et al. 2006; Nowicki et al. 2010; Cupisti et al. 2011). Self reported PA is also correlated with serum albumin (Li et al. 2010) but more modestly than objective PA measures. In addition, accelerometer estimated minutes of MVPA and average PA intensity are moderately correlated with energy and protein intake of HD patients (Cupisti et al. 2011). Serum creatinine (a gross marker of muscle mass) is positively associated with self-reported PA (Wong et al. 2011) and indices of objectively estimated PA including steps taken, total EE (Avesani et al. 2012) and activity counts (Johansen et al. 2000; Johansen et al. 2001a; Hung et al. 2002). Importantly, protein energy wasting is reported to interact with inflammation and increase CV mortality risk threefold among maintenance HD patients (de Mutsert et al. 2008).

Although relationships with risk factors are based on cross-sectional data there is overwhelming evidence that many of these are amenable to behavioural intervention in the general population. Meta-analytical reviews show structured or habitual PA reduces visceral adiposity (Ismail et al. 2012), improves lipid profile and lowers triglycerides (Monda et al. 2009), decreases risk of developing diabetes (Gillies et al. 2007), and lowers blood pressure (Whelton et al. 2002). Moreover, a Cochrane review of PA interventions indicates similar improvement in some of these health status indices for the stage 5 CKD population (Heiwe and Jacobsen 2011).

There is general agreement that self-reported PA correlates with quality of life indicated by Medical Outcomes Short-Form 36 (MOS SF-36) and SF-12 scores from

single-centre (Brenner and Brohart 2008; Li et al. 2010) and large multi-centre (Johansen et al. 2010b) studies involving HD patients. Habitual PA is also inversely associated with fatigue among maintenance HD patients (Bonner et al. 2010; Gordon et al. 2011). Moreover, multivariable analysis by Gordon et al. (2011) suggested that objectively estimated PA explained the greatest proportion of shared variance in post-dialysis fatigue while self-reported PA was not independently associated. Anaemia status is also a contributor to fatigue and there is agreement that the former is independently predictive of PA level derived via objective (Johansen et al. 2000; Zamojska et al. 2006) but not subjective measures (Johansen et al. 2010b; Wong et al. 2011). In addition, maintenance HD patients who achieve consensus PA guidelines are 94% less likely to have cognitive dysfunction compared to sedentary patients (Stringuetta-Belik et al. 2012).

1.2.1.17 Sedentary behaviour and health outcomes

While the importance of PA is well documented, accumulating evidence indicates sedentary behaviour is not simply the flipside of the same coin. In the general population, clear dose-response relationships between self-reported sitting time and increased mortality risk have been documented in large epidemiological studies with follow up periods of 6.6 to 21 years (Inoue et al. 2008; Katzmarzyk et al. 2009; Dunstan et al. 2010, Wijndaele et al. 2010; Warren et al. 2010). Notably, the Canada Fitness Survey found the association between sedentary time and CV and all-cause mortality remained significant regardless of whether participants were classified as active or inactive (Katzmarzyk et al. 2009). Self-reported time spent seated is independently associated with subclinical CVD (Kozàkovà et al. 2010) and health biomarkers (Celis-Morales et al. 2012). Moreover, the latter were more strongly correlated with accelerometer estimated sitting time (Celis-Morales et al. 2012). Sedentary time, as well as breaks in sedentary time, estimated via Actigraph accelerometers are significantly correlated with markers of metabolic risk (Healy et al. 2007; Healy et al. 2008b; Gaya et al. 2009; Helmerhorst et al. 2009) independent of PA level. Studies of enforced curtailment of PA with active (non-exercising) men over two weeks (Olsen et al. 2008; Krogh-Madsen et al. 2010), and 3 days of bedrest (Smorawiński et al. 2000) show significant adverse effects on metabolic indices and visceral fat. Although protocols in these studies are imperfect models of sedentary behaviour they demonstrate the deleterious effects that even short-term increases in this metric can exert.

Clearly, people with stage 5 CKD at greatest risk of premature mortality are those categorised as sedentary defined as one or fewer exercise bouts/week (O'Hare et al. 2003; Tentori et al. 2010), or inactive defined as the lowest tertile of PA (Zelle al. 2011; Rosas et al. 2012). However, such categorisations are not completely congruent with the currently agreed working definition of sedentary behaviour as:

''Any waking behaviour characterized by an energy expenditure of ≤1.5 metabolic equivalents (METs) while in a sitting or reclining posture''

(Sedentary Behaviour Research Network 2012, p. 540).

Review of the current literature reveals a remarkable absence of data exploring sedentary time and its relationship with health outcomes in stage 5 CKD.

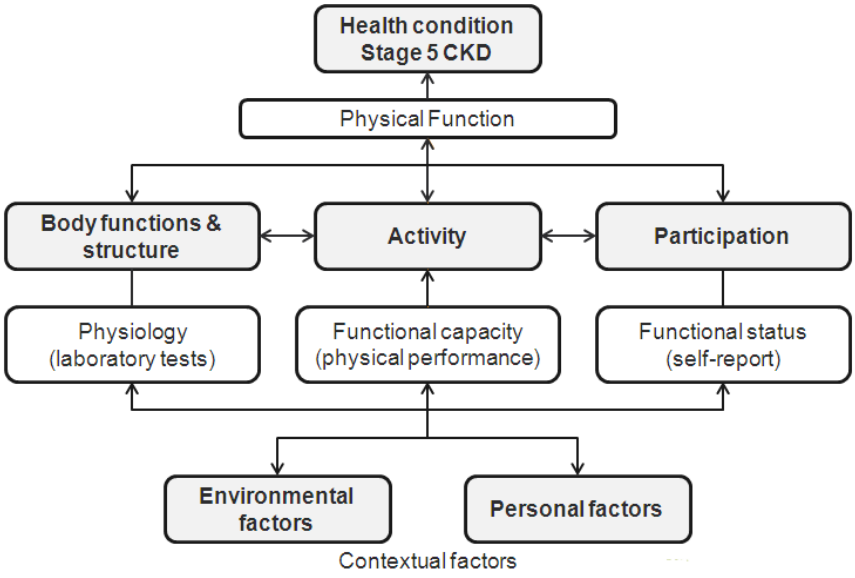
1.2.1.18 Summary

There is overwhelming evidence that PA is implicated in survival and important health outcomes of people with stage 5 CKD. Large-scale epidemiological studies attest to the prognostic utility of self-reported PA in this population. However, smaller studies employing objective PA measures show comparatively stronger associations with numerous putative risk factors for morbidity and mortality. As well as helping elucidate why PA is prognostic of outcomes, activity monitors have provided comparatively greater insight into activity patterns of maintenance HD patients. Maintenance HD patients are beset by lower levels of PA but the true scale of low PA in this population is likely greater than has been reported. Physical activity counselling is recommended as part of health management for this population, however there is little guidance to support renal healthcare providers in implementing this recommendation.

1.2.2 Epidemiology of physical function in stage 5 CKD

The International Classification of Functioning, Disability and Health (ICF) model was developed by the World Health Organisation (WHO 2001) to clarify confusion of terms and concepts related to physical functioning (Freedman 2009). Figure 1.8 describes the ICF framework in which physical function is an umbrella term composed of three levels of increasing complexity. Physical function refers to an individual's physiological status, ability to perform activities of daily life and more complex leisure time pursuits and roles that include social integration. There is considerable evidence that stage 5 CKD is characterised by severely reduced PF across all three levels of the ICF model and that this is closely linked to health outcomes and quality of life.

Figure 1.8 International classification of functioning, disability and health (WHO 2001) adapted for stage 5 CKD.



1.2.2.1 Impaired physical function status in stage 5 CKD

Several reviews concur that cardiorespiratory fitness (CRF) of haemodialysis (HD) participants is on average 60 to 70% of age predicted VO_{2peak} values (Cheema and Singh 2005; Johansen 2007; Parsons and King-Van Vlack 2009; Segura-Orti 2010; Smart and Steele 2011). Dynamometry measures of lower limb muscle strength (table 1.9) are 22 to 45% lower than asymptomatic controls (Johansen et al. 2003a; Blake and O'Meara 2004) and age-predicted values (Bohannon et al. 1995; Boudeville et al. 2010). In addition hand-grip strength (HGS) of maintenance HD patients is 20 to 76% lower compared to age-equivalent norm values (Qureshi et al.

1998; Stenvinkel et al. 2002; Nascimento et al. 2004; Silva et al. 2011), peritoneal dialysis (Wang et al. 2005) and predialysis patients (Pagels et al. 2008) (table 1.9).

Estimates of functional capacity obtained via physical performance tests also indicate profound impairment (table 1.10). Proxy measures of CRF for middle-aged HD patients (Greenwood et al. 2012; Lane et al. 2013) are a staggering 61% reference values for adults aged over 70 years (Harrison et al. 2013) and 41% lower than people with chronic heart failure (Pulz et al. 2008). Walk test estimates of endurance (Painter et al. 2000; Ling et al. 2003; Bullani et al. 2011; Ragnarsdottir et al. 2012) are 10 to 32 % lower than norm values for adults 10 - 25 years older (Steffen and Seney 2002) with an even greater disparity observed for senior adults (Jamal et al. 2006). Gait speed of HD patients is 18 to 34% slower than healthy controls (Johansen et al. 2003a; Blake and O'Meara 2004) and norm values (Bohannon et al. 1995; Painter et al. 2000; Johansen et al. 2001a; Johansen et al. 2003a). Worryingly, 65% of participants in the study of Painter et al. (2000) were slower than a key prognostic threshold of 1.0 m/s. Surrogate measures of lower limb neuromuscular function also reflect values of more aged individuals (table 1.10). Chair stand performances of younger HD patients (Blake and O'Meara 2004) are closer to norm values for adults over 60 (Bohannon et al. 2006a), while middle-aged individuals (Johansen et al. 2001a; Johansen et al. 2003a) are still 10 to 12% slower than healthy octogenarians (Bohannon 2006a). Similarly, functional mobility is 4 to 18% slower than asymptomatic adults 10 – 20 years more senior (Jamal et al. 2006; Bullani et al. 2011; Greenwood et al. 2012; Ragnarsdottir et al. 2012). Moreover, prevalence of poor functional mobility among older HD patients is reported to be an alarming 80% (Cook and Jassal 2010).

Significant deficits are also apparent at the participation level of the ICF model. The Dialysis Mortality and Morbidity Study (DMMS) revealed 42% of North American dialysis patients reported severe limitations with activities of moderate intensity (Stack and Murthy 2008). There is overwhelming agreement from large-scale studies that regardless of whether functional status is characterised by subscales from quality of life questionnaires or dedicated instruments, outcome values are well below age expected norms (DeOreo 1997; Painter et al. 2000; Tawney et al. 2000; Mapes et al. 2003; Johansen et al 2010b). Moreover, functional status of all 1547 participants in the Comprehensive Dialysis Study (CDC) was at or below the 50th percentile for healthy adults aged over 70, while almost 95% had transformed scores that equated to low aerobic fitness (Johansen et al. 2010b).

Table 1.9 Severity of impaired muscle fitness in stage 5 CKD (body structure and function level of ICF).

Study	Sample (n)	Age	M/F	Tests	Mean values	Norm or control value comparison
Su et al. 2012	Prevalent HD (274)	60.7 ± 11.7	36/64	HGS (Kg)	All 20.9 ± 9.6	No values by gender
Silva et al. 2011	Prevalent HD (436)	47.3 ±14.2	63/37	HGS (Kg)	Men 29.1 ± 8.7 Women 19.4 ± 6.5	↓47% ↓43%
Boudeville et al. 2010	Prevalent HD (25)	69.8 ± 12.1	80/20	Knee extensor force	19 kg (5 - 46 kg)	Non-uraemic participants 35 - 58 kg
Pagels et al. 2008	Pre-dialysis (116)	63.0 ± 15.0	68/32	HGS (Kg)	Men 37.1 ± 10.2 Women 20.4 ± 6.6	↓11% ↓21%
Jamal et al. 2006	Prevalent HD (52)	66.0 ± 9.0	71/29	HGS (Kg)	All 21.5 ± 9.3	No values by gender
Wang et al. 2005	Prevalent PD (233)	55.0 ± 12.0	51/49	HGS (Kg)	All 19.9 ± 10.6 Men 24.8 ± 10.3 Women 14.7 ± 8.1	 ↓44% ↓51%
Blake and O'Meara 2004	Prevalent HD (12)	42.0 ± 8.5	58/42	Knee extensor Isometric Peak torque (N) Knee extensor Isokinetic peak torque (N) Time to peak (s)	134.3 ± 62.8 61.8 ± 33.3 6.8 ± 2.7	Compared to 12 controls 203 ± 59.8, 34% lower ($p < 0.05$) 111.8 ± 43.3, 45% lower ($p < 0.005$) 5.0 ± 2.8 ($p = 0.10$)
Nascimento et al. 2004	Prevalent HD (109)	53.0 ± 12.0	62/38	HGS (Kg)	Not stated	All ↓25%, Men ↓29%, Women ↓19% Well nourished ↓17%, Malnourished ↓38%
Johansen et al. 2003a	Prevalent HD (22)	55.0 ± 15.0	53/47	Leg Dorsiflexors Isometric peak MVC (N)	169.6 ± 65.5	↓22% compared to 17 controls ($p = 0.03$)
Stenvinkel et al. 2002	Prevalent HD (206)	52.0 ± 10.0	61/39	HGS (Kg)	Men 37 ± 1 Women 23 ± 1	↓27% ↓26%
Qureshi et al. 1998	Prevalent HD (128)	57 (26-79) 68 (32-85) 64 (33-83)	59/41	HGS (Kg) well nourished mildly malnourished mod-severe malnourished	Men 34 ± 12 Women 22 ± 9 Men 24 ± 9 Women 13 ± 7 Men 12 ± 11 Women 11 ± 6	↓31% Compared to 44 controls ↓19% ↓51% ↓52% ↓76% ↓59%
Bohannon et al. 1995	Prevalent HD/PD (110)	45.1 ± 11.6	69/31	Non-dominant knee extensor force (N) Dominant knee extensor force (N)	309.3 ± 120.5 317.0 ± 119.6	33.2% lower than controls (472.6 ± 89.8) 34.6% lower than controls (474.8 ± 88.2)

Table 1.10 Impaired functional capacity in stage 5 CKD (activity level of ICF).

Study	Sample (n)	Age (yrs)	M/F %	Tests	Mean values	Norm or control values
Lane et al. 2013	Prevalent HD (42)	44 ± 5	62/38	ISWT (m)	251 ± 120	↓61% (>70 yrs, Harrison et al. 2013)
Greenwood et al. 2012	Prevalent HD (128)	56.6 ± 12.2	48/52	ISWT (m) TUAG (s) STS 60 (reps) Stair climb & descend (s)	247.7 ± 137.1 10.2 ± 11.0 19.3 ± 7.1 29.9 ± 21.0	↓61% (>70 yrs, Harrison et al 2013) ↑11% (> 70-79yrs, Bohannon 2006b) No normative data No normative data
Ragnarsdottir et al. 2012	Prevalent HD (21)	69 (37-88)	Not stated	6MWT (m) TUAG (s) STS10 (s)	275 (90-452) 13 (5.4-33) 44 (22.9-58.4)	↓32% (>80 yrs, Steffen et al. 2002) ↑41% (70-79yrs, Bohannon 2006b) ↑128% (Csuka and McCarty 1985)
Bullani et al. 2011	Prevalent HD (11)	70 ± 10.7	73/27	6MWT (m) TUAG (s)	307 ± 155 12.1 ± 6.6	↓24% (>80 yrs, Steffen et al. 2002) ↑7% (>80 yrs, Bohannon 2006b)
Cook and Jassal 2010	Prevalent HD (130)	74.8 ± 5.9	57/43	TUAG (s)	Not stated	80% >10 sec
Nonoyama et al. 2010	Prevalent HD (10)	68.1 ± 7.1	78/22	2MWT (m) TUAG (s)	96.8 ± 44.2 14.2 ± 7.1	↓36% (Connelly and Thomas 2009) ↑46% (70-79yrs, Bohannon 2006b)
Jamal et al. 2006	Prevalent HD (52)	66.0 ± 9.0	71/29	6 MWT (m) TUAG (s)	109m ± 58 13.6 (9.9-17.4)	↓73% (>80 yrs, Steffen et al. 2002) ↑48% (70-79yrs, Bohannon 2006b)
Sterky and Stegmayr 2005	Prevalent HD (11)	75 (60-82)	91/9	STS10 seconds (reps) Stair climb/descend (reps)	3.4 4	↓50% compared to 22 controls ↓54% compared to 22 controls
Blake and O'Meara 2004	Prevalent HD (12)	42.0 ± 8.5	58/42	Average gait speed (m/s) Max walk speed (m/s) STS5 (reps)	1.31 ± 0.12 1.74 ± 0.18 10.1 ± 0.16	↓18% ($p < 0.005$) compared to 12 controls ↓15% ($p = 0.01$) compared to 12 controls ↑38% ($p < 0.001$) compared to 12 controls
Johansen et al. 2003a	Prevalent HD (38)	55 ± 15	53/47	Average gait speed (cm/s)	100.2 ± 33.2	↓33% ($p < 0.001$) compared to 19 controls
Johansen et al. 2003c	Incident HD (54)	51.5 ± 17	67/33	Average gait speed (cm/s) STS 5 (s) Stair Climb (s)	112.8 ± 34.5 16.3 ± 9.3 10.0 ± 7.5	↓21% (50-59 yrs, Bohannon 2011) ↑10% (>80 years, Bohannon 2006a) No normative data
Ling et al. 2003	Prevalent HD & PD (72)	52.8 ± 9.8	Not stated	TUAG (s) 6MWT (m)	9.6 ± 3.7 368.8 ± 97	↑4% (Bohannon 2006b) ↓10% (80-89yrs, Steffen et al. 2002)
Johansen et al. 2001a	Incident HD (46)	52 ± 17	67/33	Average gait speed (cm/s) STS 5 (s) Stair Climb (s)	113.1 ± 34.5 16.6 ± 9.5 10.3 ± 7.7	↓19% slower than predicted 139.3 ± 4.7 ↑12% (>80 years, Bohannon 2006a) No normative data
Painter et al. 2000	Prevalent HD (205)	56.6 ± 15.6	44/57	Gait speed (cm/s) STS10 (s) 6MWT (m)	90.5 ± 25.6 29.3 ± 12.5 347.0 ± 127.1	34% slower than predicted norm 75% slower than predicted norm ↓14% (80-89 yrs, Steffen et al. 2002)
Bohannon et al. 1995	Prevalent HD & PD (110)	45.1 ± 11.6	69/31	Average gait speed (cm/s) Max gait speed (cm/s) STS 10 seconds (reps)	109.1 ± 21 176 ± 45.6 5.8 ± 2.0	↓23% compared to predicted (141.1 ± 5.1) ↓20% compared to predicted (221.3 ± 17.3) No normative data

Impaired PF ultimately manifests itself in reduced participation and disability, the scale of which was first revealed by Gutman et al. (1981), who found just 23 to 60% of HD patients (diabetic and non-diabetic respectively) engaged in activities more strenuous than basic self-care. Worryingly, these findings are just as relevant today as prevalence of disability with one or more basic activities of daily living (feeding, dressing, grooming, ambulation, toileting and bathing) is still 41% among HD patients of all ages (McAdams-Demarco et al. 2012) compared to 5.0 to 8.1% for community dwelling older adults (Wiener et al. 1990).

1.2.2.2 Assessment of physical function in stage 5 CKD

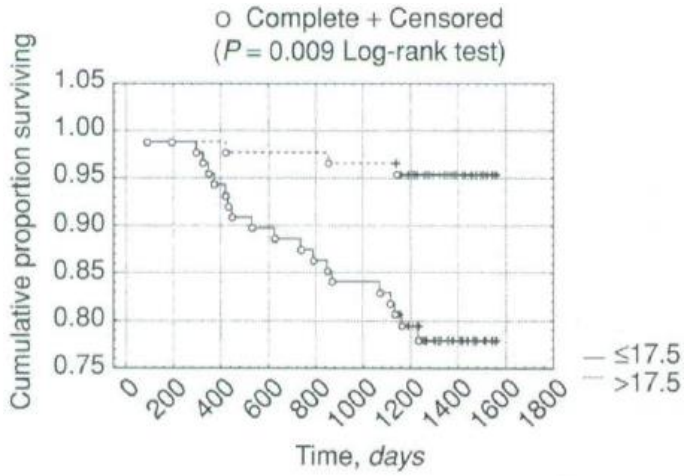
In light of the high prevalence of PF impairment in stage 5 CKD routine monitoring of physical function is recommended in section 14.3 of the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) as part of health management (NKF 2005). Regular PF assessment is compatible with the shift towards 'person-focused' care, which implies more comprehensive recognition, knowledge and care of the individual's problems as well as their primary diagnosis (Starfield 2011). The value of PF assessment lies in being able to: identify individuals at risk of poor outcomes who may benefit from further medical evaluation or preventive interventions by monitoring over time; stratifying risk for surgery or other interventions; evaluating the effectiveness of interventions or clinical trials (Koufaki and Kouidi 2010). In addition, there is growing recognition of the deleterious effects of frailty on health outcomes in this population a condition that is not exclusive to gerontology but also highly prevalent in stage 5 CKD (Johansen et al. 2007; Bao et al. 2012; McAdams-Demarco et al 2013; Painter et al. 2013). Furthermore, it is argued that consistent use of physical function outcomes for kidney transplant candidates could yield improved post-transplant outcomes (Kutner et al. 2006) and use of healthcare resources (Houle et al. 2002).

Although routine PF assessment is strongly indicated there is little to support renal healthcare providers in operationalising KDOQI recommendations except for a broad statement suggesting use of physical performance testing or questionnaires. Importantly, if PF assessment is to be adopted as part of standard clinical practice or employed in research it must meet certain scientific criteria outlined by Lohr et al. (1996): validity (does it measure what it claims to measure?); utility (does the measure have prognostic and discriminatory usefulness in the clinical setting?); reproducibility (are repeat measures similar enough to be consistent?);

responsiveness (is the measure sensitive enough to track changes over time?). Fulfilment of these criteria is crucial in order that healthcare providers can invest in outcomes that will benefit their patients. The following section will review PF assessment methods employed in stage 5 CKD according to the ICF framework.

Gold standard cardiopulmonary exercise tests (CPET) have often been used to measure exercise tolerance for exercise intervention programmes in stage 5 CKD (Johansen 2007; Parsons and King-van Vlack 2009; Smart and Steele 2011). The seminal paper of Sietsema et al. (2004) is frequently cited as an example of the prognostic utility of CRF in this population. A VO_{2peak} value above 17.5 ml/kg/min (5 METs) obtained via cardiopulmonary exercise test (CPET) was independently associated with improved survival in a cohort of 175 prevalent HD patients over a mean follow up of 3.5 years. Participants below this threshold had significantly greater mortality compared to those above it (22% and 5% respectively).

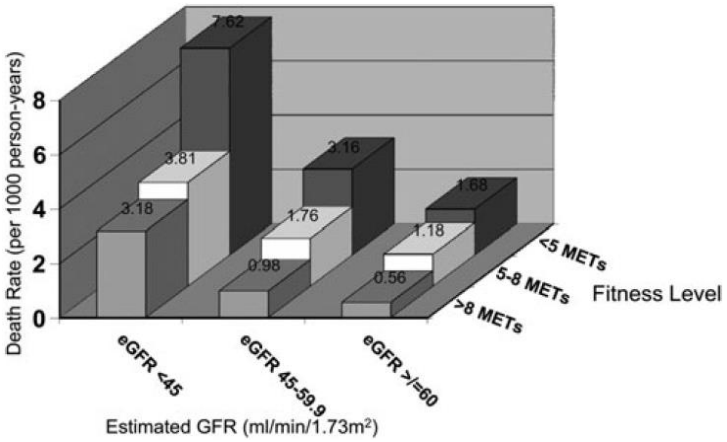
Figure 1.9 Survival of maintenance HD patients as a function of baseline VO_{2peak} (Sietsema et al. 2004, p. 721).



Although these findings were derived from relatively young and healthy HD patients (46 ± 13 years) with a comparatively low overall mortality rate (13%) this threshold appears to be robust for different levels of renal impairment. A study of 5716 middle-aged women (52.5 years ± 10.8) found a CRF below 5 METs was independently associated with the highest mortality risk at every level of estimated GFR over a 16 year follow up period (Gulati et al. 2012). Moreover, even though all-cause mortality increased with declining GFR in the cited study, CRF continued to significantly modify the relationship between renal function and mortality. In addition, peak aerobic power also shows moderate to strong inverse associations with depression

scores of HD patients (r = -0.53 to -0.64, p < 0.01) (Carney et al. 1986), which affects 20 - 26% of this population (Hedayati et al. 2009; Fischer et al. 2010).

Figure 1.10 Mortality rates stratified by eGFR and cardiorespiratory fitness level (Gulati et al. 2012, p. 922).



Upper limb muscle fitness is commonly measured via hand grip dynamometry, while lower limb measures are less common (table 1.9), likely due to the former being easier to obtain. Three-year survival among 126 middle aged (52 ± 1.0 years) incident male HD patients was higher for participants whose isometric HGS was above the median value (Stenvinkel et al. 2002), however the precise value was not reported. Notably, this outcome measure is also predictive of disability, as well as CV and all-cause mortality among older adults and people with less severe CKD (Al Snih et al. 2002; Qureshi et al. 2002; Rantanen et al. 2003). Hand-grip strength is also prognostic of nutritional status (indicated by lean body mass) in HD (Stenvinkel et al. 2002) and PD cohorts (Wang et al. 2005; Dong et al. 2008) and is independently predictive of malnutrition among predialysis patients (Heimburger et al. 2000). Moreover, declining HGS of HD patients relative to predicted values (Nascimento et al. 2004) and controls (Qureshi et al. 1998) (table 1.9) was associated with level of malnutrition indicated by subjective global assessment. Hand-grip strength was also independently and inversely associated with malnutrition and inflammation score in a large cohort of 436 maintenance HD patients (Silva et al. 2011).

Maximum aerobic power (VO_{2peak}) determined by CPET is considered to provide the most valid measure of CRF. However, reproducibility of this outcome shows appreciable intra-individual variability in older adults (Greig et al. 1994) and clinical

populations such as CHF (Bensimhon et al. 2008) and stage 5 CKD (Koufaki et al. 2001). Furthermore, although it is predictive of mortality risk, CPET measured CRF may not necessarily indicate ability to perform essential ADLs requiring lower effort for longer periods (Koufaki and Mercer 2006; Johansen 2007). In addition, although physiological indices may provide invaluable data regarding the mechanisms of functional impairment, their relationship with meaningful person-centred outcomes such as functional status and falls is not well defined. Furthermore, laboratory tests carry significant burden in terms of equipment, time, specialised personnel, expense and space, and do not lend themselves well to routine clinical use.

1.2.2.3 Physical performance tests

Feasible proxy measures of cardiorespiratory and neuromuscular fitness are obtained via physical performance tests, which are more cost effective, require less equipment and are easily administered. Tests of functional capacity where individuals determine their exertion level correspond to the activity level of the ICF framework. Tasks are designed to approximate activities commonly encountered during daily life and arguably have greater construct validity in capturing activity impairment. Moreover they are an important determinant of functional status and disability in stage 5 CKD (Cook and Jassal 2008).

Chair stand tests that replicate the ability to transfer have frequently been employed in HD studies as surrogate measures of lower limb neuromuscular function (table 1.10). The sit-to-stand 5 (STS5) test (Guralnik et al. 1994) which records the time taken to complete five transfers from a standardised chair height has well documented psychometric properties (table 1.11) and is increasingly being used in CKD research. Good to excellent reproducibility has been observed among community dwelling elderly (Schaubert and Bohannon 2005; Bohannon et al. 2007; Tiedeman et al. 2008) and people with stage 5 CKD (Koufaki et al. 2002). Test performance is moderately correlated with lower limb muscle strength of elderly asymptomatic individuals (Lord et al. 2002; McCarthy et al 2004) and people with stage 5 CKD (Bohannon et al. 1995). In addition strong correlations have been observed with other prognostic physical performance measures including average gait speed and the timed up-and-go test (Merretta et al. 2006; Schaubert and Bohannon 2007). Importantly the STS5 has clinical utility with a cutpoint range of 10 and 15 seconds predicative of falls risk (Tiedeman et al. 2008; Buatois et al. 2010) and balance dysfunction (Whitney et al. 2005).

Table 1.11 Psychometric properties of sit-to-stand 5 test.

Psychometric Property	Value	Population	Author
Minimum detectable difference	4.2 seconds	Healthy community dwelling elderly n = 10, age 75.5 ± 5.8 years	Schaubert and Bohannon 2005
Minimum clinically important difference	2.3 seconds for improved Dizziness Handicap Inventory score	Balance disorders n = 117, age 62.7 years	Meretta et al. 2006
Prognostic utility	>12 seconds Further falls risk assessment indicated	Community dwelling elderly, n = 362, age 74-98 years	Tiedemann et al. 2008
	>15 seconds. Falls risk ratio = 1.74, CI: 1.24– 2.45 (p<0.001). Follow up 1.5 to 3 years	Community dwelling elderly, n = 1958, age 70 ± 4 years.	Buatois et al. 2010
	>10 seconds. Balance dysfunction (<60 yrs) >14.2 seconds. Balance dysfunction (>60 yrs)	Balance disorders n = 93. Age matched controls n = 81	Whitney et al. 2005
Test –retest reliability	ICC = 0.81, CI not stated. CV = 16.85% Interval 0, 6, 12 weeks	Community dwelling elderly. n = 10, age 75.5 ± 5.8 yrs.	Schaubert and Bohannon 2005
	ICC = 0.89, 95% CI = 0.79, 0.95. Interval 12 months	Community dwelling elderly. n = 362, age 80.4 ± 4.5 yrs	Tiedemann et al. 2008
	ICC = 0.96, CI not stated	Asymptomatic adults. n=94	Bohannon et al. 2007
	Intra-session CV = 15.1%	Stage 5 CKD 5, n = 33	Koufaki et al. 2002
Construct Validity	Correlation with isokinetic strength of hip flexors, knee extensors, ankle plantarflexors, r = -0.58, -0.46, -0.58 respectively, (p < 0.01)	Women. n = 46, 64.5 ± 3.1	McCarthy et al. 2004
	Correlation with knee flexion and extension isometric force r = -0.43 (p < 0.01)	Community dwelling elderly. n = 669, 78.9 ± 4.1 years	Lord et al. 2002
	Knee extension isometric force: dominant r = 0.59, non-dominant r = -0.64 (p < 0.001)	Stage 5 CKD. n = 110, age 45.1 ± 11.6 years.	Bohannon et al. 1995
Convergent Validity	Correlation with TUAG r = 0.59 (p < 0.01) Correlation with gait speed r = 0.53 (p < 0.01)	Balance disorders n = 117, age 62.7 years	Meretta 2006
	Correlation with TUAG r = 0.92 (p < 0.05) Correlation with gait speed r = 0.94 (p < 0.01)	Healthy community dwelling elderly n = 10, age 75.5 ± 5.8 years	Schaubert and Bohannon 2005
Responsiveness	Responsiveness-treatment coefficient = 0.58	Balance disorders. n = 117	Meretta et al. 2006

Table 1.12 Psychometric properties of Timed up-and-go test.

Psychometric Property	Value	Population	Author
Reliability	Intra session test-retest reliability ICC = 0.97 (CI not stated).	Community dwelling elderly. n = 96, age 73 ± 8 years	Steffen et al. 2002
	Test-retest reliability ICC = 0.97, follow up 2 months Interrater reliability ICC 0.99 (CI not stated)	Older adults. n = 20 79.5 years Older adults. N = 22	Podsiadlo and Richardson 1991
	Intrarater Reliability ICC = 0.92 (CI = 0.86 - 0.95) Interrater Reliability ICC = 0.91 (CI = 0.86 - 0.94)	Elderly in residential care. n = 78, age 84.8 ± 5.7 years	Nordin et al. 2006,
Prognostic utility	>12.3 secs. Falls. Sensitivity 83%, specificity 97%	Community dwelling older adults, n = 35. 72.9 ± 7.8 yrs.	Wrisley and Kumar 2010
	>13.5 secs. Falls, sensitivity 87%, specificity 87%.	Non-fallers, n = 15, age 78 ± 6 yrs. Fallers, n = 15, age 86 ± 6 yrs.	Shumway-Cook et al. 2000
	>10 secs independently associated with 6.64 (CI 2.24-19.71) higher odds ratio of dependency with one or more core ADLs.	Maintenance HD patients. n = 162, age 74.8 ± 5.9 yrs	Cook and Jassal 2008
	1 second increments = 8% increase in mortality risk over median 3 year follow up.	CKD stage 2 to 4. n = 385, age 61 ± 13 years.	Roshanraven et al. 2013
Construct validity	BERG balance scale r = -0.81, gait speed r = -0.61, (p value not stated).	Community dwelling older adults. n = 60, age 79.5 years	Podsiadlo and Richardson 1991
	Functional gait assessment , r = 0.84, ($p < 0.001$)	Community dwelling older adults, n = 35. 72.9 ± 7.8 yrs.	Wrisley and Kumar 2010
	Correlation with Tinetti Balance, Tinetti Gait, walking speed r = -0.55, -0.53, 0.66 respectively (p value not stated).	Community dwelling older adults, n = 1200, mean age 73.4 years	Lin et al. 2004
Convergent validity	Two minute walk test r = -0.68, Functional Independence Measure r = -0.59 ($p < 0.001$), Functional reach r = -0.36 (p = 0.02)	Senior adults inpatient rehab, n = 52, age 80 ± 8 years.	Brooks et al. 2006
	Barthel index r = -0.78 (p value not stated)	Community dwelling older adults. n = 60, age 79.5 years	Podsiadlo and Richardson 1991
	Correlation with Older Adults Resources and Services ADL scale r = -0.45 (p value not stated)	Community dwelling older adults, n = 1200, age 73.4 years	Lin et al. 2004
Responsiveness	Moderate effect for ADL decline (ES = 0.42) Small effect for ADL improvements (ES = 0.05) Small effect for falls (ES = 0.12)	Community dwelling older adults, n = 1200, age 73.4 years	Lin et al. 2004

The STS5 is also a component of the short physical performance battery commonly used to evaluate lower limb function in the elderly (Guralnik et al. 1994) and has well established age-equivalent norm values (Bohannon 2006a). Other variations of this test exist such as the sit-to-stand 10 and longer 30 and 60 second protocols in which the number of transfers is counted. Longer duration tests such as the sit-to-stand 60 are proposed as indicators of lower limb muscle endurance and fatigability (McCarthy et al. 2004) and the latter has been used in a number of exercise studies involving HD patients (Cappy et al. 1999; Koufaki et al. 2002; Majchrzak et al. 2005; McIntyre et al. 2006; Cook et al. 2008). Test performance is strongly correlated with self-reported nutritional status (Mercer et al. 2004) and thigh muscle cross-sectional area of people with stage 5 CKD (McIntyre et al. 2006). The STS60 demonstrates clinically acceptable reliability in this population (Koufaki et al. 2002; Segura-Orti and Martinez-Olmos 2011). However, as with the STS10 and STS30, there is no data regarding prognostic utility or agreed norm values for any of these test variations.

The timed up-and-go (TUAG), which measures the time taken to stand up from a chair, walk out three metres, return and sit (Podsiadlo and Richardson 1991) is a physical performance test commonly used in clinical practice. The TUAG is proposed as a composite measure of lower limb strength, balance and gait (Bischoff et al. 2003). Generally regarded as an indicator of functional mobility the test sequentially simulates demands on the neuromuscular and balance systems commonly encountered during daily activities (Bischoff et al. 2003; Podsiadlo and Richardson 1991).

Psychometric properties of the TUAG are also well documented (table 1.12). Intraclass correlation coefficients are excellent for test reproducibility (Podsiadlo and Richardson 1991; Steffen et al. 2002) and inter-rater reliability (Shumway-Cook et al. 2000; Nordin et al. 2006) in asymptomatic adults. Convergent validity has been observed with other physical performance measures of endurance (Brooks et al. 2006), lower limb strength (Meretta et al. 2006), balance and gait speed as well as functional status (Podsiadlo and Richardson 1991; Lin et al. 2001). The TUAG is also well supported with age-equivalent norm values established by a meta-analytical review (Bohannon 2006b).

Notably, a TUAG time over 10 seconds is independently associated with an almost sevenfold risk of dependency with one or more basic activities of daily living (ADL) among senior HD patients (Cook and Jassal 2008). Moreover, test duration above

this threshold is predictive of future placement in long term care for older adults (Nikolaus et al. 1996). This may be especially salient in light of prevalence of slow TUAG times being as high as 80% among older HD patients (Cook and Jassal 2010). Importantly, there is agreement that a test time above 12 seconds is highly accurate in identifying community dwelling older adults with a history of falls (Shumway-Cook et al. 2000; Wrisley and Kumar 2010). Such prognostic utility might be considered invaluable in a population beset by higher incidence of falls among older adults compared to the general population (12.7% versus 4% respectively) (Desmet et al. 2004; Hestekin et al. 2013). In addition, it may also explain in part why the TUAG has greater discriminative ability than bone mineral density testing in detecting bone fractures among older adults receiving HD therapy (Jamal et al. 2006). Importantly, increments of 1 second are independently associated with an attendant 8% increased risk of mortality over 3 years among people with less severe CKD (Roshanraven et al. 2013).

Various walking tests have been employed to assess exercise tolerance in stage 5 CKD without the need for expensive equipment and specialised personnel. These physical performance tests are relevant for people with low functional capacity as they replicate the most common form of daily activity. The six-minute walk test (6MWT) has been employed in several stage 5 CKD studies, and the 2 minute walk test less frequently (table 1.10). Psychometric properties are well supported and there are indications the 6MWT is at least as prognostic of health outcomes in CKD as the TUAG (Jamal et al. 2006; Roshanraven et al. 2013). Other walk tests employing stair climb and/or descent such as the North Staffordshire Royal Infirmary walk test (Mercer et al. 1998) have also shown clinically acceptable psychometric properties for people with stage 5 CKD. However, low use stairs and space required for the 6MWT may not always be available in a hospital environment potentially limiting feasibility of these tests. In addition, walk tests requiring a self-selected gait speed for a pre-specified time or distance are susceptible to variations in pacing judgement, mood and motivation.

More recently the incremental shuttle walk test (ISWT) (Singh et al. 1992), which is an externally paced, symptom limited walking test has been increasingly adopted as a functional capacity outcome in stage 5 CKD (Wilund et al. 2010; Greenwood et al. 2012; Lane et al. 2013). The test requires limited space (10 metres) and equipment (CD player and two marker cones), and elicits a graded cardiovascular response (unlike the 6MWT) with incrementally quicker walking speeds. In addition, theoretical

Table 1.13 Psychometric qualities of the incremental shuttle walk test.

Psychometric Property	Value	Population	Author
Minimum clinically important difference	47.5 metres, CI: 38.6 to 56.5 metres	Chronic obstructive pulmonary disease (COPD), n = 372, age 69.4 ± 8.4 years.	Singh et al. 2008
Prognostic utility	<450 m: tertile with lowest 12 month event-free survival (36%) ($p < 0.01$)	Class 2-4 Heart failure, n = 53, age 53 ± 10 years	Morales et al.1999
Reliability	Test-retest ICC = 0.80 CI: 0.62 to 0.90 (8 week interval)	Stable CVD patients, n = 30, age 67 ± 8 years.	Pepera et al. 2010
	Intra-session test-retest difference 29.5 m, CI: 23.0 to 36.0 ($p < 0.001$). ICC = 0.94, CI not stated.	Cardiac rehabilitation, n = 353, age 61.6 ± 10.2 years	Jolly et al. 2008
	Intra-session test-retest difference 7.0 m , CI: -33.0 to 47.0 ($p > 0.05$)	Chronic heart failure (CHF) grade 2-4, n = 63, age 51.3 ± 10.2 years	Pulz et al. 2008
	Pearson's r = 0.90, $p < 0.001$	Heart transplant candidates, n = 25, age 53 ± 8 years	Lewis et al. 2001
	Intra-session Pearson's $r = 0.98$, $p < 0.01$	CHF grade 2 - 4, n = 7, 52.4 ± 3.2 years.	Green et al. 2001
	ICC = 0.87 CI not stated, CV 15.9%	Intermittant claudication, n = 55, age 68 (52–80) years	Zwierska et al. 2004
Validity	VO_{2peak} r = 0.93, SEE 2.8mL/kg/min ($p < 0.01$)	CKD 5, n = 22, age 57 ± 17.4 years	Mercer et al. 2011
	Treadmill VO_{2peak} r = 0.83, Ambulatory VO_{2peak} during ISWT r = 0.78 ($p < 0.05$)	CHF grade 2 - 4, n = 7, 56.7 ± 1.5 years.	Green et al. 2001
	VO_{2max} r = 0.81 to 0.88, (p value not stated	COPD 2 samples, n = 19 age 61 ± 7 years, and n = 10, age 64 ± 7 years.	Singh et al. 1994
	VO_{2peak} r = 0.73, $p < 0.001$). Discriminatory power >360-430m predicts VO_{2peak} >14 ml O_2/kg/min. Sensitivity 75%, specificity 77%	Heart transplant candidates, n = 25, age 53 ± 8 years	Lewis et al. 2001
	VO_{2max} r = 0.83, ($p < 0.001$). >450 m predicts VO_{2max} > 14 ml O_2/kg/min, sensitivity and specificity not stated.	CHF grade 2 - 4, n = 46, age 53 ± 10 years	Morales et al. 1999
Responsiveness	Standardised response mean: 1.18 for antibiotics	Cystic Fibrosis, n = 24, 30.3 ± 15.3 years.	Bradley et al. 2000

peak oxygen consumption can be calculated from terminal walking speed using a formula developed by the American College of Sports Medicine (ACSM 2010). The ISWT is considered a feasible proxy measure of CRF compared to CPET measured VO_{2peak}. Although originally developed for people with chronic obstructive airways disease the ISWT has been employed in other clinical populations. It exhibits clinically acceptable psychometric qualities and has been validated in stage 5 CKD (table 1.13). Moreover, the ISWT is supported by comprehensive age-stratified normative values for the UK population (Harrison et al. 2013). Data regarding prognostic utility of the ISWT are limited to individuals with chronic heart failure (Pulz et al. 2008). However, there are indications that test performance may be linked to mortality risk via intermediate CV vectors. Wilund et al. (2010) found change in ISWT performance was inversely associated with epicardial fat ($r = -0.66$, $P = 0.01$) a marker of CVD presence and severity in a small study of 15 HD patients. Moreover, moderate inverse associations have been observed between the ISWT and indices of central arterial stiffness of maintenance HD patients (Lane et al. 2013), which is strongly predictive of CV and all-cause mortality in this population (Blacher et al. 2003; Verbeke et al. 2011).

Lastly, high prevalence of slow self-selected gait speed is also well documented in stage 5 CKD (Bohannon et al. 1997; Painter et al. 2000; Johansen et al. 2001a; Johansen et al. 2003b; Blake and O'Meara 2004). Not only is an ambulation speed of 1.2 m/s required to cross a pedestrian crossing safely (Asher et al. 2012), a gait below 1.0 m/s is significantly associated with reduced survival among community dwelling older adults (Abellan van Kan et al. 2009; Afilalo et al. 2010). Moreover, a 0.1 m/s reduction in gait speed is associated with an incremental 26% increase in adjusted mortality risk over three years in stage 2 - 4 CKD (Roshanraven et al. 2013).

1.2.2.4 Self-reported physical function in stage 5 CKD

Impact of reduced physical performance ultimately manifests itself in reduced participation in social activities and functional disability, which is associated with the third level of physical function of the ICF framework. Large-scale studies attest to the predictive utility of patient reported functional status in the dialysis population. The Dialysis Morbidity and Mortality Wave 2 study (DMMS) revealed mortality risk was 75% higher over 3.6 years for incident HD patients reporting severe limitations with moderate intensity activities (Stack et al. 2005). McClellan et al. (1991) were

Table 1.14 Functional status and health outcomes in stage 5 CKD.

Study / outcome	Sample (*n*)	Age ± SD	M/F %	Period	Mean score ± SD	Findings (adjusted or stated if not)
McClellan et al. 1991 Karnofsky Performance scale	Incident HD & PD (294)	56.6 ± 15.1	51.2/48.8	1.3 yrs	7.06 ± 0.11	First year survival: Lowest quartile 55.7% highest quartile 94.5% ($p < 0.001$).Mortality risk relative to no impairment: mild (2.4, CI 0.66-3.64), moderate (6.1, CI: 1.78-20.74), severe (14.5, CI: 4.7 – 41.3) ($p < 0.001$). 1 unit = 28% change mortality risk (0.61-2.01)
DeOreo 1997 MOS SF-36	Incident HD (1000)	58.2 ± 15.4	50/50	1.5 yrs	PCS[1] 44.3 ± 27.8 MCS[2] 47.9 ± 11.6	PCS < 34.6, relative risk mortality = 2.03 (1.44-2.85, $p < 0.001$), hospitalisation = 1.67 (1.43-1.95, $p < 0.001$). 5 point PCS change = 10.4% change in survival (0.6 – 19.0, $p = 0.04$)
Ifudu et al. 1998 Modified Karnofsky	Prevalent HD (522)	59.0 ± 15.0	48.3/51.7	3 yrs	Not stated	Score <70, unadjusted relative risk of mortality 44% (1.24 – 1.68, $p < 0.001$)
Kalantar-Zadeh et al. 2001 MOS SF-36	Prevalent HD (65)	54.5 ± 15.8	53.8/46.2	1 yr	PCS 48.8 ± 18.8 MCS 55.7 ± 18.4	10 point decrease total SF-36 score = hazard ratio 2.03 (1.08 – 3.98, $p = 0.024$). PCS not independently predictive of mortality ($p = 0.14$) 10 point PCS decrease: relative risk first hospitalisation 23% (1.01 to 1.51, $p = 0.048$). PCS correlated with hospitalisation days ($r = -0.28$) and frequency ($r = -0.40$), nutrition ($r = -0.10$), BMI ($r = -0.35$), albumin ($r = -0.29$), haemoglobin ($r = -0.27$), ($p < 0.01$).
Lowrie et al. 2003 MOS SF-36	Prevalent HD (13952)	59.0 ± 15.4	51.4/48.6	6 mths	PCS 33.3 ± 10.5 MCS 47.5 ± 11.7	1 point PCS reduction = 2% higher mortality risk (CI 0.969-0.982, $p < 0.001$) 1 point PCS increase = 2% lower hospitalisation risk (CI and p value not stated)
Mapes et al. 2003 KDQOL-SF	Incident HD (10030)	58.9 ± 14.9	57.4/42.6	3.4 yrs	PCS 35.3 ± 10.8 MCS 44.9 ± 11.9	Lowest PCS quintile (Score < 25) relative mortality risk = 1.93 (CI not stated, $p< 0.001$), hospitalisation 1.53 (CI not stated, $p < 0.001$) 10 point change PCS = 29% higher mortality risk (1.23-1.35, $p < 0.001$), 15% relative risk hospitalisation (1.11-1.18, $p < 0.001$).
Knight et al. 2003 MOS SF-36	Incident HD (5773)	61.0 ± 15.4	54/46	2 yrs	PCS 31.6 ± 9.8 MCS 46.0 ± 11.3	10 point decline in PCS = 25% higher mortality risk at 1 year (1.18 – 1.33, p value not stated)
Feroze et al. 2011 MOS-SF36	Prevalent HD (705)	53.5 ± 14.7	53/47	6 yrs	Not stated	Lowest PCS quartile (Score < 37.2) hazard ratio = 1.45 (1.0-2.1, $p < 0.05$). **10 point PCS change = 8% change in relative mortality risk** (1.02-1.15, $p < 0.05$). PCS correlated with BMI ($r = -0.10$), albumin ($r = 0.21$), creatinine ($r = 0.25$), CRP ($r = -0.13$), HD vintage ($r = 0.08$)

[1] PCS physical component summary score
[2] MCS mental component summary score

the first to explore the relationship between functional status and survival in stage 5 CKD using the Karnofsky Performance Status (KPS) scale (Karnofsky et al. 1948). The study found mortality risk at one year more than doubled for each level of progressively greater functional impairment. However, the KPS questionnaire was designed for oncology palliative care, and there are no data regarding its psychometric properties in the CKD population. The scale is completed by a health professional, and therefore it may not actually capture the individual's perceived level of physical function.

The physical component summary score (PCS) derived from the Medical Outcomes Study Short Form-36 (MOS SF-36) (Ware and Sherbourne 1992) or the Kidney Disease Quality of Life Short Form (KDQOL-SF) (Hays et al. 1994) which has the SF-36 at its core, is commonly used to indicate functional status (table 1.14). As with the SF-36, KDQOL-SF item scores are aggregated without weighting and transformed linearly to a 0-100 range from which the PCS is derived. Higher scores indicate better functional status. Psychometric properties are well documented in the dialysis population with clinically acceptable levels of reliability, responsiveness, content and construct validity for both the SF-36 (Mingardi et al. 1999; Gomez-Besteiro et al. 2004) and KDQOL-SF (Hays et al. 1994; Korevaar et al. 2002; Park et al 2007; Bataclan and Dial 2009).

Since the study of McClellan et al. (1991) functional status and mortality has been explored several times using the PCS from the MOS SF-36 questionnaire (table 1.14). Participants with a PCS less than the median score (34.6) were twice as likely to die and 1.5 times more likely to be hospitalised compared to those at or above the median score over 1.5 years (DeOreo 1997). Similar findings were reported for the lowest quintile of PCS scores obtained via the KDQOL-SF in the much larger international Dialysis Outcomes and Practice Pattern Study (Mapes et al. 2003). Notably the study of Knight et al. (2003) found a 10 point reduction in PCS over 6 months after HD initiation was independently associated with a 25% higher risk of death at one year (Knight et al. 2003).

In general 5 point increments in PCS score are consistently associated with increases in adjusted mortality risk of 10-15% (table 1.14) among incident (DeOreo et al 1997; Mapes et al. 2003) and prevalent dialysis patients (Lowrie et al. 2003). Risk of hospitalisation for the same change in outcome score is broadly similar (Kalentar-Zadeh et al. 2001; Lowrie et al. 2003; Mapes et al. 2003). Notably,

functional status is reported to be as significant a predictor of mortality risk as clinical indices of health status such as dialysis adequacy (Kt/V), normalised protein catabolic rate, and albumin (DeOreo 1997; Mapes et al. 2003; Feroze et al. 2011). Moreover, PCS scores in the DOPPS study were independently associated with greater risk of hospitalisation while important clinical markers such as albumin were not (Mapes et al. 2003). Self-reported function is also correlated albeit modestly with clinical markers of health status including BMI, haemoglobin, nutritional status, and CRP (Kalantar-Zadeh et al. 2001; Lowrie et al. 2003; Feroze et al. 2011).

Perhaps a disadvantage of the SF-36 and KDQOL-SF is the completion time required. The Duke Activity Status Index (DASI) (Hlatky et al. 1989), a short questionnaire comprising 12 activity items weighted according to their physiological cost has also been employed to monitor functional status in stage 5 CKD (Cook et al 2008; Nonoyama et al. 2010; Greenwood et al. 2012). The Duke was initially validated in cardiac patients using CPET obtained VO_{2max} (Pearson's r = 0.58 to 0.81, $p < 0.001$) by Hlatky et al. (1989). Subsequent studies have demonstrated fair to moderate criterion validity (Pearson's r = 0.31 to 0.65) in a number of clinical populations (Merz et al. 2000; Carter et al. 2002; Struthers et al. 2008) including CKD (Ravani et al. 2012). Internal consistency is high (Cronbachs alpha = 0.86, Von Dras et al. 1997) and the Duke has shown clinically acceptable reproducibility in CKD (Ravani et al. 2012). Notably CRF scores derived from the Duke are independently predictive of fatal and non-fatal cardiac events in women with symptomatic coronary artery disease over 5 years (Shaw et al. 2006). Prognostic utility observed in a cardiac population and expediency could conceivably lend the DASI to CV risk stratification in stage 5 CKD.

Independent associations between functional status and survival have not been observed in every study and this may be due to their smaller size (Kalantar-Zadeh et al. 2001) and modification of the functional status outcome (Ifudu et al. 1998). However, the weight of evidence from studies adjusted for multiple demographic and clinical variables supports the prognostic utility of self-reported functional status in stage 5 CKD. A limitation of these observational studies is their inability to determine causation. Low functional status may therefore be a marker of disease severity or comorbidity burden, and reflect those who are destined to have higher mortality rates. This relationship could be bi-directional with functional disability impacting important aspects of health like nutritional status. For example HD patients unable to undertake shopping and cooking independently are more than

two and a half times more likely to be malnourished than those able to perform these activities (Sehgal et al. 1998).

An advantage of functional status measures is their ability to capture individuals' perceptions of their capability to perform activities of daily living (ADLs) or engage in leisure pursuits in a way that objective methods cannot. Moreover, they are cost effective, expedient and can be administered to people unable to undertake physical performance tests. There is increasing recognition of person-centred outcomes to complement traditional clinical outcomes such as mortality, non-fatal events, hospital admissions, and healthcare cost (Liem et al. 2007; Valderas et al. 2008). However, by virtue of their subjective nature questionnaire responses are susceptible to influences such as temporal variations in symptoms (Lyons et al. 1999; Nelson-Danquah et al. 2010), cognitive impairment (Guralnik et al. 2001), and education level (Koufaki and Koudi 2010). Psychosocial factors influence both physical performance and self reported function but there are indications their relative contribution to the latter is greater (Carmichael et al. 2000; Lord et al. 2002; Bean et al. 2011). Moreover, reliability of self-reported physical function is comparatively lower than physical performance measures (Davey et al. 2003; Overend et al. 2010).

1.2.2.5 Physical function, disability and frailty in stage 5 CKD

Importantly, declining PF is part of a process leading to functional disability, increased healthcare burden and also ADL dependency (Cook and Jassal 2008), placement in private care and in-hospital mortality (Sood et al. 2011). Worryingly, disability with one or more basic ADLs in the study of McAdams-Demarco et al. (2012) was associated with a more than threefold higher adjusted risk of premature mortality compared to HD patients without disability. There is growing recognition of the importance of undiagnosed frailty on health outcomes of HD patients (Painter et al 2013). Frailty among incident HD patients is independently associated with a 50% higher risk of hospitalisations and a two to threefold increased risk of mortality among incident and prevalent HD patients over one and three years respectively (Johansen et al. 2007; McAdams-Demarco et al 2013). Importantly three of the five core components of Fried's frailty phenotype (Fried et al. 2001) may be obtained from measures of physical performance (muscle weakness, slow gait) and functional status (exhaustion) measures. Early identification of frailty facilitated by routine PF monitoring may therefore play an important role in early identification of

at risk individuals. Timely interventions could then be targeted to ameliorate functional decline and reduce risk of hospitalisations and mortality in the HD population.

This review shows there is overwhelming evidence of high prevalence of severe PF impairment in stage 5 CKD. Not only is the disparity between maintenance HD patients and age-matched peers (or reference values) alarming in magnitude, in many cases reported physical function is even lower than non-uraemic individuals two decades more senior. Physical function assessment in this population shows little standardisation with numerous subjective and objective measures employed (summarised in table 1.15). Importantly, there is general agreement that physiological indicators of function and self-reported functional status are predictive of numerous health outcomes in this population. Prognostic utility of physical performance tests is largely inferred from findings in the general population and is an area that requires further exploration in people with stage 5 CKD. Importantly there is an absence of research regarding the responsiveness of PF outcome measures to PA change in stage 5 CKD.

Table 1.15 Measurement of physical function in stage 5 CKD.

Precision & Reliability: Higher / Lower

ICF level	Cardiorespiratory function	Neuromuscular function
Body structure & function (Physiology)	VO_{2peak} obtained via cardio-pulmonary exercise test	Leg dynamometry Grip strength
Activity (functional capacity)	Incremental shuttle walk test 6 minute walk test 2 minute walk Stair climb/descent NSRI walk	Chair rise tests: STS5; STS10; STS 30; STS60; Average gait speed Maximum gait speed Timed up-and-go
Participation (functional status)	SF-36/KDQOL-SF physical component score Duke activity status index Human activity profile Karnofsky Performance Status scale	

Feasibility & Expediency: Lower / Higher

1.2.2.6 Physical function and physical activity in stage 5 CKD

It has been suggested that the reason why physical function is predictive of health outcomes in stage 5 CKD is because it is likely to be associated with physical activity/exercise behaviour (Kutner et al. 2000; Johansen et al. 2001a). Worryingly, low levels of PA are highly prevalent in stage 5 CKD (Johansen et al. 2001b; Stack

and Murthy 2008; Tentori et al. 2010) with only a small percentage (13%) achieving recommended PA levels (Painter et al. 2011). This is due in part to HD patients enduring extended periods of enforced sitting during dialysis, accumulating an additional 12 to 15 hours per week. Moreover, fatigue associated with uraemia and the HD procedure and multi-morbidity add up to form a potent triad, which contribute to high prevalence of sedentary behaviour. The deleterious effects of inactivity on muscle mass and strength on healthy individuals are well documented in bedrest studies (Kortebein et al. 2007; Ikezoe et al. 2011). Furthermore, inactivity per se is a low-grade inflammatory state, which inhibits muscle protein synthesis, a key mechanism, which leads to muscle atrophy (Guadagni and Biolo 2009).

Aerobic activities which comprise most habitual daily PA may not offer the same level of hypertrophy that resistance exercise does but there is evidence that the former do stimulate muscle protein synthesis (Sheffield-Moore et al. 2004; Bechshoeft et al. 2012). In addition, although genetic heritability is reported to explain around 55% of the variance in CRF, recent PA is the largest modifiable enviromental determinant (Bouchard and Perusse 2005). High prevalence of sedentary behaviour in stage 5 CKD likely explains in part the severity and scale of PF impairment observed. Encouragement of PA by renal staff forms part of KDOQI recommendations (NKF 2005) presumably based on the premise that this form of lifestyle intervention will improve physical function. Candidate assessment methods for routine monitoring of physical function should therefore be sensitive to change in PA as well as having prognostic utility. Although PA is believed to underpin aspects of physical function there is a paucity of information regarding which measures may adequately reflect behavioural change in stage 5 CKD.

To date, just two studies have explored the association between PA and physical function in stage 5 CKD (Johansen et al. 2001a; Kutsuna et al. 2010). In both studies habitual PA determined objectively by accelerometry was independently associated with average gait speed. Notably, Kutsuna et al. (2010) found that a minimum of 50 minutes of total PA per day above 1.8 METs was sufficient to prevent deterioration of gait speed in a sample of 157 maintenance HD patients. Johansen et al. (2001a) observed that HD dosage indicated by Kt/V was also an independent predictor of average gait speed, chair rise and stair climb performance. The inference being that greater dialysis dosage may improve functional capacity. However, a more recent study did not find physical performance measured by short physical performance battery was improved with greater nocturnal dialysis

frequency (Hall et al. 2012). Importantly, the modest sample size (n = 39) in the study of Johansen et al. (2001a) did not meet the minimum requirement for multiple regression analysis (n = 50 + number of candidate variables) outlined by Harris (1985) increasing the risk of a type II error. Moreover accelerometer data reduction criteria were not explicitly stated, which may have adversely affected integrity of the PA data and attenuated associations with the physical performance outcomes.

Implications of such research considerations are important as findings may inadvertently dissuade healthcare providers from seeing PA recommendations as complementary to medical management of health in stage 5 CKD. Re-visiting clinical, demographic and behavioural correlates of PF across a wider spectrum of physical performance tests in a larger cohort of maintenance HD patients is therefore warranted. Lastly, prognostic utility of self reported physical function in stage 5 CKD is well documented, however as with physical performance there is limited research exploring the correlates functional status questionnaires in this population. Gender, comorbidity status, albumin and age were independently associated with PCS scores from the KDQOL-SF in the international DOPPS project (Lopes et al. 2007). However, the relative contribution of PA to functional status of maintenance HD patients has thus far not been explored.

1.2.2.7 Summary and research questions

There is overwhelming evidence that low physical function is highly prevalent in stage 5 CKD and that it is associated with health outcomes across all three levels of the ICF framework. Routine monitoring of physical function is recommended in addition to traditional clinical indicators to augment health management of this population. However there is little in the way of constructive guidelines to support health professionals with selection of suitable physical function outcomes that have clinical utility and are sensitive to behavioural change. Research in this area is strongly indicated in order that routine monitoring of functional level may be feasibly implemented in stage 5 CKD and outcomes standardised.

What are the correlates of physical performance measures of physical function in stage 5 CKD?

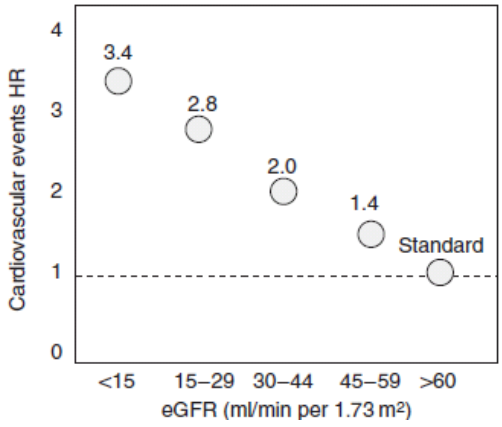
What are the correlates of self-reported physical function in stage 5 CKD?

What is the relative contribution of physical activity to physical performance and self-reported measures of physical function in stage 5 CKD?

1.2.3 Epidemiology of arterial stiffness in stage 5 CKD

There is overwhelming agreement from renal registry data in different countries that high mortality and morbidity in the haemodialysis (HD) population is driven by cardiovascular (CV) causes (UKRR 2012; USRDS 2011, SRRR 2013). Depending on country CV disease accounts for 33-52% of all mortality among people receiving maintenance HD (Uchida et al. 2007; Breidthardt et al. 2011; USRDS 2012; UKRR 2012; SRRR 2013), with sudden cardiac death accounting for almost 30% (Herzog et al. 2008a). Alarmingly, incidence of myocardial infarction and stroke is three to fifteen times higher in stage 5 CKD compared to the general population (Parfrey et al. 1996, Go et al 2004, Tonelli et al 2006). Moreover, CKD is an established CV risk factor (Sarnak et al. 2003) with a graded inverse association between glomerular filtration rate, and risk of CV events and hospitalisations (figure 1.11) (Zoccali et al. 2011; Briet et al. 2006; Go et al. 2004).

Figure 1.11 Relationship between renal function and risk of CV events (Zoccali et al. 2011, p. 3).



Increased presence of focal plaques and occlusive lesions (atherosclerosis) of the intima (surface) layer of the arteries may mediate higher CV risk in stage 5 CKD. Autopsy findings show atherosclerotic changes in the aortae of HD patients are more severe compared to age and gender matched individuals with CVD with an eGFR of >60 mL/min/1.73m^2 (Suzuki et al. 2011). Moreover, a large ultrasound study demonstrated prevalence and severity of carotid artery plaques was highest among individuals on dialysis compared to people with stages 1 to 3 CKD and normal renal function (78%, 56% and 43% respectively) (Coll et al. 2010). Interestingly, multivariable modeling in the latter study confirmed traditional risk factors rather than CKD related variables were predictors of aortic atherosclerosis.

However, disproportionately high CV mortality and morbidity in the stage 5 CKD population is not explained by the presence of traditional CV risk factors such as diabetes, smoking, BMI and elevated serum cholesterol (Zoccali 2000; Longenecker et al. 2002). Moreover a “U” shaped relationship exists between blood pressure and mortality risk in this population (Zager et al. 1998). Aggressive pharmacotherapy of traditional risk factors is a cornerstone of CV health management in the general population but it does not appear to have the same efficacy in ameliorating CVD burden in stage 5 CKD. Large-scale randomized control trials have found no significant difference in mortality and CV events for HD patients receiving statin therapy compared to those who did not (Kalantar-Zadeh et al. 2003; Wanner et al 2005). Moreover, long-term prognosis remains poor even after myocardial revascularization via percutaneous stenting or bypass graft (Herzog et al. 2008b). Consequently atherosclerosis, is believed to be only partially responsible for high CVD morbidity and mortality in stage 5 CKD (London et al 2002).

1.2.3.1 Haemodynamic consequences of arterial stiffness

Attention has increasingly focused on the deleterious haemodynamic implications of reduced compliance of large capacitive arteries. Increased arterial stiffness is believed to be the principal mechanism for isolated systolic hypertension whereby reduced compliance results in early wave reflections, augmenting systolic afterload and a widening of pulse pressure (O’Rourke & Hashimoto 2007; London et al. 1996). The other outcome of increased arterial stiffness is impaired coronary perfusion during diastole leading to subendocardial ischaemia (O’Rourke & Hashimoto 2007; Wang et al. 2007). Although the relationship between blood pressure and mortality in stage 5 CKD differs to non-uraemic individuals, large-scale studies concur severely abberant systolic and diastolic blood pressure is independently predictive of survival over four years (Iseki et al. 1997; Zager et al. 1998)

The pulsatile work of the heart is consequently increased and it is believed chronically elevated systolic pressure mediates pathological concentric hypertrophy of the left ventricle. There is consensus that indices of central arterial stiffness are independently associated with left ventricular mass and cardiac wall thickness of adolescents and young adults (Toprak et al 2009; Urbina et al. 2011), diabetics (Henry et al 2004), maintenance HD patients (Marchais et al 1993; Nitta et al. 2004) and people with less severe CKD (Wang et al. 2007). Although the cited studies are

cross-sectional further support for role of arterial stiffness in deleterious cardiac remodeling comes from aggressive blood pressure management studies. Concomitant decreases in left ventricular mass have been observed with reductions in central arterial stiffness during year-long interventions in essential hypertension (Shimamoto and Shimamoto 1996) and stage 5 CKD (London et al. 1994; Suzuki et al 2003).

Worryingly, left ventricular hypertrophy (LVH) is present in 75% of people with CKD by the time HD is initiated (Foley et al. 1995), and prevalence reportedly increases to 90% thereafter (London et al. 2001b). Moreover, increasing severity of LVH, and in particular, ventricular dilation is greatest over the first year of dialysis (Foley et al. 1998). Abnormal LV dilation and systolic dysfunction are independently associated with the development of ischaemic heart disease subsequent to initiation of HD as well as a threefold higher risk of heart failure (Parfrey et al. 1996). In addition, LVH in patients with hypertension is associated with features that promote myocardial conduction instability and ventricular arrhythmias (Zoccali 2010) and sudden cardiac death. The presence of LVH is independently predictive of CV and all-cause mortality of HD patients over three years (Silberberg et al. 1989; Zoccali et al. 2001; London et al. 2001b).

1.2.3.2 Measurement of arterial stiffness

Non-invasive measurement of central arterial stiffness is increasingly being employed as part of health research targeting CV health. An expert consensus document recommends carotid-femoral (aortic) pulse wave velocity (PWV) as the 'gold standard' for measurement of central arterial stiffness (Laurent et al. 2006). Pulse wave velocity is calculated by measuring the time taken for the pressure wave to travel between two selected sites after ventricular ejection (arterial path length divided by transit time). Pulse wave velocity is calculated via the Moens-Korteweg equation (equation 2.1), where k is a constant, E is the vessel wall elastic modulus, h is wall thickness and R is lumen diameter. Higher velocities indicate greater aortic stiffness.

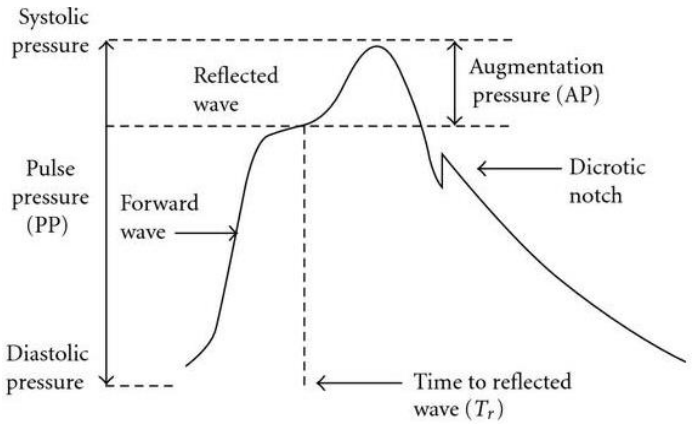
Equation 2.1 Moens-Korteweg equation for pulse wave velocity.

$$PWV = k(Eh/R)^{1/2} \qquad \text{(Safar and Frohlich 2007)}$$

Augmentation index is another vascular stiffness measure, which represents the impact of waves reflected from the periphery mainly at branch points (or sites of impedance mismatch) on the ascending aortic pressure waveform (O'Rourke and

Kelly 1993). The difference between the early and late systolic peaks of the systolic pulse wave contour, known as augmentation pressure (AP) is divided by the pulse pressure (difference between systolic and diastolic pressure) in order to derive a percentage increase value (O'Rourke and Kelly 1993). Considered a composite measure of central arterial stiffness and peripheral pulse wave reflections (Safar et al. 2003), higher values also indicate stiffer vessels.

Figure 1.12 Components of pressure wave analysis for calculation of AI (adapted from Stoner et al. 2014).



Techniques for measuring arterial stiffness in stage 5 CKD vary. Doppler probes were initially used (tables 1.16 and 1.17), while later studies have employed devices utilising applanation tonometry (SphygmoCor®, AtCor Medical, Victoria, Australia) or mechano-transducers (Complior SP®, Artech medical, Pantin, France), which have been validated invasively (Laurent et al. 2006). Arterial stiffness outcomes from these machines are highly reproducible in CKD (Shoji et al. 2001; Sigrist et al. 2010; Avramovski et al. 2013) and asymptomatic populations (Papaioannou et al. 2007), however, they are expensive and require specialised training. The Vicorder® (Skidmore Medical Ltd, Bristol, UK) is a more recent device that employs oscillometry to measure arterial stiffness with similar reliability (Hickson et al. 2009; Kis et al. 2011). There is general agreement that Vicorder underestimates PWV relative to SphygmoCor at higher arterial stiffness values (Hickson et al. 2009; van Leeuwen-Segarceanu et al 2010; Kis et al. 2011; Shahin et al 2013) but agreement can be improved with a correction equation (Hickson et al. 2009). Additional advantages of the Vicorder system are that it is automated and thus largely operator independent, as well as being comparatively more portable and lower cost.

1.2.3.3 Prognostic utility of arterial stiffness in stage 5 CKD

Prospective observational studies agree that regardless of measurement device employed higher aortic PWV is predictive of premature mortality among people receiving dialysis after adjustment for traditional CV risk factors (table 1.16). Moreover, there is consensus that risk of all-cause mortality, as well as fatal and non-fatal CV events is 15% higher for every 1 m/s increment in PWV (Shoji et al. 2001; London et al. 2001a; Blacher et al. 2003, Pannier et al. 2005; Verbeke et al. 2011). This is in agreement with a meta-analytic review, which found that risk of all-cause mortality and CV events was 14 to 15% higher for the same increment across 15,877 participants followed up over an average of 7.7 years (Vlachopoulos et al. 2010). In contrast, Blacher et al (1999) reported a markedly higher risk of 39% but it is possible the authors may have reported the risk associated with one standard deviation of the mean PWV as opposed to 1 m/s.

Individuals receiving HD who are in the highest tertile of PWV experience the greatest mortality burden (Blacher et al. 1999; London et al. 2001a; Verbeke et al. 2011), and a PWV value equal to or exceeding 11 m/s appears to be a crucial threshold (London et al. 2001a; Pannier et al. 2005). While PWV may also be obtained from the femoral and brachial arteries it appears only aortic values have prognostic utility in this population (Pannier et al. 2005). Augmentation index, is also predictive of outcomes but this has only been demonstrated in the study of London et al. (2001a). Cox's proportional hazard models from these studies also indicated age, gender, diabetes and dialysis vintage were predictive of CV outcomes with the notable exception of blood pressure indices (Blacher et al. 1999; Shoji et al. 2001; Blacher et al. 2003; Pannier et al. 2005; Verbeke et al. 2011).

Arterial stiffness may simply be a marker of established CVD and reflect the higher disease burden of people 'destined' for premature death. However, associations with adverse changes in cardiac morphology (Marchais et al. 1993; London et al 1996; Nitta et al. 2004) suggest that changes in aortic structural properties likely pre-figure the development of clinically overt CVD. Consequently, arterial stiffness indices offer a novel means by which CVD risk may be monitored. Although AI and aortic PWV are both proposed as arterial stiffness outcomes they may not be used interchangeably (Laurent et al. 2006). Importantly, intervention studies for targeting vascular health in CKD are increasingly using one or both of these outcomes (Mustata et al. 2004; Toussaint et al. 2008a; Koh et al. 2010; Mustata et al. 2011).

Table 1.16 Prognostic utility of indices of arterial stiffness in stage 5 CKD.

Study	Study Sample (n)	Age	M/F (%)	DM (%)	HD vintage	Index & Device	Value	Period (mths)	Findings
Verbeke 2011	HD & PD (1076) Event No event	 59.2 68.1	 59/41 62/38	 17 29	 28 30	Aortic PWV SphygmoCor	 9.5 11.8	24	**PWV 1 m/s**: All cause mortality and non-fatal CV events **RR = 1.15** (CI 1.08 to 1.23, p < 0.001) **PWV > 12 m/s** vs < 8.8 m/s **HR 1.94** (CI 1.38 – 2.73, p value not stated)
Pannier 2005	HD (305)	53 ±16	Not stated	10	Not stated	Aortic PWV Doppler	11.1 ±3.1	70 ± 49	**1 m/s** increase in PWV **CV mortality** adjusted **RR 1.12** (CI 1.03–1.25, p not stated) **PWV cutoff** for increased **CV mortality 10.75 m/s**, (84% sensitivity, 73% specificity, 87% negative predictive value, 72% positive predictive value.
Blacher 2003	HD (242) no previous CVD	52 ±16	61/39	7	49 ±54	Aortic PWV Doppler	Not stated	78 ± 46	**PWV 1 m/s**: **All cause mortality**: crude RR = 1.34 (1.23–1.47); adjusted **RR 1.14** (CI 1.03–1.26) (p = 0.02) **CV mortality**: crude RR 1.34 (1.24–1.44); adjusted **RR 1.14** (1.05–1.24) (p = 0.02)
London 2001a	HD (180)	54 ±16	60/40	10	59 ±64	AI (%) Aortic PWV Doppler	26.0 ±15 11.7 ±3.0	52 ± 36	**Augmentation Index 10%**: All cause mortality adjusted **RR = 1.51** (CI 1.23 - 1.86, p = 0.0001); CV mortality **RR = 1.48** (CI 1.16 - 1.90; *p* = 0.002). **AI cut-off** for increased **all cause mortality 24.5%** (sensitivity 83%, specificity 67%, AUC 0.74 ± 0.04) **AI cut-off** for increased **CV mortality 25%** (sensitivity 80%, specificity 70%, AUC 0.82 ± 0.05) **PWV 1 m/s**: **All cause mortality** adjusted **RR = 1.16** (CI 1.06 - 1.28, p = 0.001); **CV mortality** adjusted **RR = 1.14** (95% CI 1.02 to 1.26; *P* = 0.02). **PWV cutoff all-cause mortality 11.5 m/s** (specificity 80%; sensitivity 74%; AUC, 0.82 ± 0.03) **CV mortality 11.3 m/s** (specificity 79%; sensitivity 64%; AUC 0.76 p = 0.04)
Shoji 2001	HD (265)	55 ±11	41/69	19	83 ±62	Aortic PWV PWV-200 Denshi	8.6 ±2.2	63 ± 23	**PWV 1 m/s**: adjusted **CV mortality OR 1.18** (CI 0.98 -1.36, p = 0.079) **PWV 1 m/s**: adjusted **all-cause mortality OR 1.16** (CI 1.03 – 1.30, p < 0.01)
Blacher 1999	HD (241)	52 ±16	61/39	7	48 ±51	Aortic PWV Doppler	11.1 ±3.1	72 ± 41	**PWV 1 m/s** adjusted **all-cause mortality OR 1.39** (CI 1.19 - 1.62, p < 0.0001). PWV tertile adjusted all-cause mortality OR: > 12.0 vs < 9.4 m/s was 5.4 (CI 2.4 - 11.9) Adjusted CV mortality OR: PWV > 12.0 vs < 9.4 m/s was 5.9 (CI, 2.3 - 5.5).

Lack of uniformity in arterial stiffness outcome may hinder meta-analytic evaluation of interventions targeting CV morbidity and mortality in the future. There is now a growing need for recommendations regarding which outcome may be the most appropriate for monitoring vascular health and effectiveness of interventions in stage 5 CKD.

1.2.3.4 Aetiology of accelerated arterial stiffness and uraemia

Aortic PWV for people with stage 5 CKD averages over 11 m/s (Blacher et al. 1999; London et al. 2001a; Pannier et al. 2005; Verbeke et al. 2011; Avramovski et al. 2013). Not only is this around 37% higher than values for middle-aged non-uraemic individuals, a PWV this high is closer to normative values observed for hypertensive seniors aged over 70 years (Mattace-Raso et al. 2010; Elias et al. 2011). Values approaching those of non-uraemic individuals have been observed, but only in a predominantly female sample (Shoji et al. 2001). Studies including a comparator group of age-matched controls confirm PWV of people with stage 5 CKD is at least 27% higher (Temmar et al. 2010; Lilitkarntakul et al. 2011; Avramovski et al 2013). In addition, cross-sectional studies indicate arterial stiffening occurs early in the disease process (Wang et al. 2005) with two thirds of people with stage 2 to 3 CKD demonstrating elevated PWV compared to controls even after adjustment for age, gender, BP, heart rate and BMI (Lilitkarntakul et al. 2011). Moreover, compared to age matched hypertensives and normotensives aortic PWV values for people with CKD are 7% and 19% higher respectively (Briet et al. 2006). Taken together there is substantial evidence that increased central arterial stiffness is a phenotype of CKD.

There is overwhelming agreement that age and blood pressure are the principal determinants of increased arterial stiffness in stage 5 CKD (table 1.17), which is in agreement with 90% of similar studies involving non-uraemic individuals (Cecilja and Chowienczyk 2009). Age-related changes in the central and conduit arteries are characterised by increases in lumen diameter and vessel wall thickness and an attendant increase in stiffness (O'Rourke and Hashimoto 2007; London et al. 2011). In addition, advancing age exerts a differential effect on the vascular system by preferentially altering the structural properties of the aorta, while distal muscular arteries are less affected (Benetos et al. 1993; Safar et al. 2005, Nichols and O'Rourke 2005). Notably, chronological age increments of 10 to 13 years are independently associated with a 1 m/s increase in aortic PWV (Avolio et al. 1983; McEniery et al. 2005).

The physiological basis for age attendant increases in arterial stiffness is mediated in part by changes in the extracellular matrix (ECM) of vessels, which consists of collagen, elastin, glycoproteins and proteoglycans (Zieman et al. 2003). Elastin cells are gradually lost or become calcified (Yu & Blumentahl 1963) and there is an overproduction of abnormal collagen cells which start to form cross-links (Greenwald 2007). In addition, degradation and fragmentation of the elastin lamellae from repetitive stress cycles subsequently places greater load on stiffer collagen fibres and changes arterial diameter (Watanabe et al. 1996; Benetos et al. 2002). Age perhaps represents the least modifiable risk factor for increased arterial stiffness. However, whether ECM changes in the arterial wall are due to the aging process *per se* or associated with long-term exposure to other risk factors for vascular aging such as diabetes, elevated blood pressure, and systemic inflammation is not yet certain (Chue et al. 2010).

The role of hypertension in hypertrophy of the arterial media to maintain tensile stress within physiological limits (Laplace's law) is well documented (equation 2.2). Animal models of induced hypertension demonstrate thickening of the media layer of the artery occurs in response to increased circumferential deformation (Dobrin 1995; Xu et al. 2000). Histological findings from autopsy studies indicate the diameter of the ascending aorta increases at a rate of 9% per decade (Watanabe et al. 1996), with an attendant doubling or tripling of the carotid artery tunica media between the ages of 20 to 90 years (Nagai et al. 1999; O'Leary et al. 1999).

Equation 2.2 Laplace's Law.

Wall stress = mean arterial pressure x arterial diameter / wall thickness

(Nichols and O'Rourke 1998)

Qualitative changes also occur in the ECM as collagen production is up-regulated at the expense of elastin, further altering the structural properties of the vessel wall (Xu et al. 2000). In addition, according to the Maxwell model, as transmural pressure rises and distends the artery there is progressively greater recruitment of collagen fibres, and a concomitant reduction in elasticity (Bank et al 1996). Furthermore, elevated blood pressure is inversely associated with endothelial function (Nigam et al. 2003), which provides functional regulation of aortic stiffness via vasomotor control (Bruno et al. 2012, McEniery et al. 2006).

Temmar et al. (2010) found diabetes was a predictor of aortic stiffness across the CKD trajectory, while plasma glucose was also associated with PWV in the

composite CKD sample of Lilitkarntakul et al. (2011). Similarly, diabetes is independently associated with arterial stiffness in just over half of published studies, explaining on average 5% of the variance (Cecilja and Chowienczyk 2009). A comprehensive review by Stehouwer et al. (2008) indicates increased arterial stiffness is a phenotype of diabetes, which is of particular importance in CKD as this is the primary renal diagnosis of at least a quarter of people starting dialysis (UKRR 2012; SRRR 2012). The role of diabetes in arterial stiffness aetiology is incompletely understood but there are several mechanisms by which insulin resistance and hyperglycaemia may directly and indirectly influence vessel properties. Hyperglycaemia mediates non-enzymatic glycation of ECM proteins forming advanced glycation end products (AGE), which subsequently increase collagen crosslinking (Lakatta 2003; Konova et al. 2004), thereby reducing elasticity and promoting vessel rigidity.

The arterial endothelium expresses a receptor for AGE (RAGE), and interaction between the two produces reactive oxygen species (Yan et al. 1994), which quench endogenous nitric oxide a potent vasorelaxant. In addition RAGE provokes increased endothelial permeability (Basta et al. 2004) and an immunological response resulting in endothelial expression of adhesion molecules and inflammatory cytokines (Basta 2008; Zhang 2008). Histological studies indicate stiff vessels are immunologically stressed showing elevated levels of cytokines, intercellular adhesion molecules, transforming growth factor-β and evidence of smooth muscle proliferation, as well as infiltration of macrophages and mono-nuclear cells (Lakatta 2003; Zieman et al 2005; Park and Lakatta 2012). Also present, are elevated levels of matrix metalloprotease and elastase enzymes associated with inflammatory regulation, which degrade the strength and elasticity of the vessel wall by fraying elastin and eliciting production of weaker collagen fibres (Wang and Lakkata 2002; McNulty et al. 2006).

The immunological response elicited by AGEs contributes to persistent low-grade inflammation that characterises stage 5 CKD, which is also implicated in endothelial dysfunction (Gunnett et al. 2005). There is agreement that impairment of this organ, which regulates vascular tone and thus the functional component of arterial stiffness is also a phenotype of diabetes (Naka et al. 2012; Tan et al. 2002; Ravikumar et al. 2002) and stage 5 CKD (van Guldener et al. 1998; Bolton et al. 2001).

Table 1.17 Variables independently associated with aortic pulse wave velocity and augmentation index in stage 5 CKD.

Study	Sample (n)	Age	M/F	Index	Independent variables	Variance explained
Lilitkarntakul et al. 2011	CKD 1-5 (CKD 5 n = 7)	48 ± 8	68/32	Aortic PWV (Sphygmocor)	Age, mean arterial pressure, high sensitivity CRP, asymmetric dimethyl arginine.	$r^2 = 0.46$ ($p < 0.05$)
Temmar et al. 2010	HD (47) CKD 4-5 (51) CKD 2-3 (52)	65 ± 13 70 ± 13 65 ± 11	60/40 63/37 58/42	Aortic PWV (Sphygmocor)	HD: Age, MAP, Diabetes, Aortic calcification score Stage 2-5 CKD: Age, MAP, Diabetes	$r^2 = 0.49$ ($p < 0.01$)
Blacher et al. 2003	HD (242) Controls (469) All (711)	52 ± 16 not stated not stated	61/39 not stated not stated	Aortic PWV (Doppler ultrasound)	Age, mean arterial pressure, heart period, gender Age, mean arterial pressure, heart period, gender Age, mean arterial pressure, heart period, gender, presence of stage 5 CKD	$r^2 = 0.57$ ($p < 0.001$) $r^2 = 0.65$ ($p < 0.001$) $r^2 = 0.62$ ($p < 0.001$)
London et al. 2001a	HD (180)	54 ± 16	not stated	AI (Applanation tonometry)	Gender, age, height, aortic PWV, left ventricular ejection time, mean blood pressure.	$r^2 = 0.49$ (p value not stated)
London et al. 1992	HD (79) Controls (73)	51.8 ± 18.6 52.7 ± 15.8	59/41 56/44	AI (Applanation tonometry)	Height, aortic PWV, left ventricular ejection time, presence of stage 5 CKD.	$r^2 = 0.58$ ($p < 0.0001$)

1.2.3.5 Vascular calcification in stage 5 CKD

A large body of evidence indicates accelerated vascular calcification (VC) plays a pivotal role in arterial stiffness of HD patients. Calcification can take place in the intima (atherosclerosis) and the tunica media of arterial walls (arteriosclerosis). Arteriosclerosis (Mönckeberg's sclerosis) is characterized by diffuse mineral deposition within the elastic lamellae of the arterial media and is distinct from intimal calcification, which is patchy, irregular and restricted to areas of atherosclerotic plaques (London et al. 2005; Mizobuchi et al 2009). Calcified atherosclerotic plaques and medial calcification of the epicardial coronary arteries are highly prevalent in adults with stage 5 CKD (Braun et al 1996; Block et al 2005). However, arteriosclerosis is a non-occlusive pathology and affects haemodynamics differently to intimal calcification by altering structural properties of the vessel walls (London et al. 2003).

Although there is a degree of heterogeneity in methods of calcification assessment and vascular section examined, commonly observed determinants of greater VC are: age, male gender, diabetes, dialysis vintage and calcium phosphate product (Taniwaki et al. 2005; Sigrist et al. 2006; Sigrist et al. 2007). Of these risk factors, considerable attention has been devoted to abnormalities of calcium and phosphate metabolism. Moreover, biochemical parameters implicated in calcification are also associated with mortality risk. High calcium, phosphorous and either high or low parathyroid hormone are independently associated with the highest mortality risk among maintenance HD patients in large retrospective Canadian studies (Block et al. 1998; Stevens et al. 2004) and the more recent DOPPS (Tentori et al. 2008). Moreover, time dependent Cox models indicate hyperphosphataemia has the greatest influence on all-cause and CV mortality (Kalantar-Zadeh et al. 2006; Noordzik et al. 2005).

There is consensus that rather than being a passive process whereby calcium-phosphate product simply exceeds solubility and precipitates, arteriosclerosis is the culmination of multiple metabolic stressors. Low-density lipid oxidation, uraemia and elevated serum phosphate precipitate the differentiation of vascular smooth muscle cells (VSMCs) into osteoblast like cells in the vessel wall (London et al. 2005; Mizobuchi et al. 2009; Nemcsik et al. 2012). Endogenous calcification inhibitors such as osteoprotegerin, matrix G1a protein, play a vital role in regulating osteoclast, osteoblast activity while pyrophosphate and Fetuin-A bind to or

sequester serum calcium and minerals to prevent crystal growth and deposition (Cozzolino et al. 2008; Mazzaferro et al. 2011).

With the exception of matrix G1a protein these calcification inhibitors are correlated with arterial stiffness in stage 5 CKD (Nemcsik et al. 2012). This may be due to potent calcification inhibitors like Fetuin-A being down-regulated by inflammation (Memoli et al. 2007), while low molecular weight solutes like pyrophosphate are possibly removed by the dialysis procedure itself (Lomashvili et al. 2005). Serum concentration of bone-morphogenetic protein-7, which prevents VSMC differentiation into cells with an osteoblast phenotype (Lund et al 2002) also declines with renal failure (Wang et al 2001). In addition, uraemia potentiated levels of fibroblast growth factor-23, a protein that regulates phosphate homeostasis and vitamin D synthesis have also been implicated (Nemcsik et al. 2012).

Figure 1.13 Mechanisms of increased arterial stiffness (image adapted from LookingForDiagnosis.com, 2014).

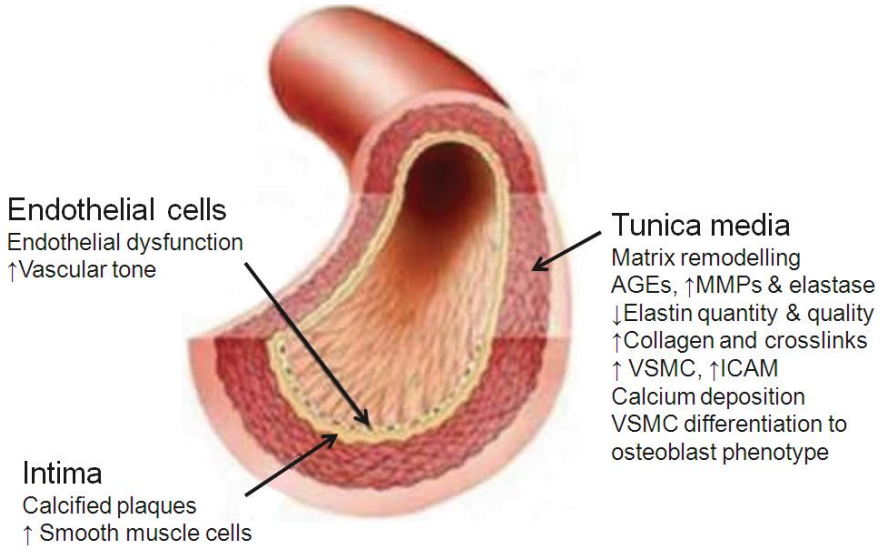


Figure abbreviations: AGE - advanced glycation end product; MMP – matrix metalloprotease; VSMC – vascular smooth muscle cell; ICAM – intracellular adhesion molecule.

As can be seen, although agreed risk factors for arterial stiffness are relatively few the underlying biological mechanisms are not only complex in the number of factors involved but also in the way they interact (McIntyre 2007). Notably, traditional CV risk factors such as smoking, cholesterol, gender and triglycerides do not appear to contribute to arterial stiffness in CKD. This is consistent with a systematic review of 77 studies by Cecilja and Chowienczyk (2009), which found the independent contribution of such risk factors was either small, or insignificant. Interestingly,

although presence of CKD is a predictor of increased arterial stiffness (London et al. 1992; Blacher et al 2003; Wang et al 2005) and incidence of CV events (Zoccali et al 2011), uraemia specific variables (serum phosphate, calcium phosphate product, dialysis dosage) are not independently associated (Lilitkarntakul et al 2011).

Pharmacotherapy has been the mainstay of vascular health management in stage 5 CKD. Reassuringly, use of non-calcium based phosphate binders halts or slows progression of coronary and aortic calcification among incident and prevalent HD patients (Chertow et al. 2002; Block et al. 2005). In addition, aggressive blood pressure management has been shown to reduce mortality risk for HD patients who respond with a decline in aortic PWV (Guerin et al. 2001).

1.2.3.6 Arterial stiffness and arteriosclerosis

Although aortic calcification occurs throughout the CKD trajectory it appears that clinically detectable signs occur only after HD initiation. There is agreement that radiograph and computerised tomography (CT) determined abdominal aorta calcification is predictive of higher PWV of maintenance HD patients (London et al; 2005; Raggi et al. 2007; Temmar et al. 2010) but not in pre-dialysis patients (Lemmos et al. 2007; Temmar et al. 2010). However, some studies have observed very modest or no association between VC and arterial stiffness in samples of HD, PD and stage 4 CKD patients (Chesterton et al 2005; Sigrist et al. 2006). Although CT imaging and scoring techniques similar to those of Temmar et al. (2010) were employed in these studies, the superior femoral artery was imaged instead, which is more muscular and less elastic than the aorta. Therefore, it might be expected that the haemodynamic effects of medial calcification at this part of the vascular tree would be less pronounced. Moreover, there is agreement that compared to other sections of the vascular tree, calcification of the abdominal aorta is more strongly associated with aortic PWV (McEniery et al. 2009; Raggi et al 2007).

Aortic calcium score determined by CT explains 3% of the variance in aortic PWV of asymptomatic adults, while age, MAP, heart rate and estimated GFR account for a further 48% (McEniery et al. 2009). The relative contribution of aortic calcification to PWV of HD patients was not quantified by Temmar et al. (2010), but it is speculated that it may be amplified given its higher prevalence and severity in stage 5 CKD. In addition, there is evidence that large artery calcification determined by CT independently predicts left ventricular mass (Nitta et al 2004) and is associated with impaired baroreceptor reflex sensitivity of HD patients (Chesterton et al 2005). The

Table 1.18 Arterial calcification in stage 5 CKD: prevalence; prognostic utility; determinants.

Study	Sample (n)	Age (yr)	M/F	HD vintage	Method	Artery	Prevalence	Findings
Verbeke et al 2011	HD & PD (1076) Event No event	 59.2 68.1	 59/41 62/38	 17 29	Lumbar radiograph. Semi-quantitative 24 point severity score	Abdominal aorta	Not stated	Fatal and non-fatal events over 2 years: Calcification severity tertile 2, RR 3.68 (CI 1.36 – 10.00, p < 0.001); tertile 3, RR 8.64 (3.53 - 21.16, p < 0.001)
Temmar et al 2010	HD (47) CKD4-5 (51) CKD2-3 (52)	65 ±13 70 ±13 65 ±11	60/49 63/37 58/42	Not reported	CT - Agatston score system >1mm > 130 hounsfield units Radiograph	Abdominal aorta	Not stated	Calcification scores highest for HD (p = 0.001) PWV determinants CKD 2 - 5: age, MAP, DM, r^2 = 0.47 HD: age, MAP, DM, Calcification score, r^2 = 0.49
Sigrist et al 2007	HD (60) PD (28) CKD 4 (46)	60 ±15 61 ±14 60 ±14	70/30 60/40 56/44	36 ±25 34 ±23	CT - Agatston score system >1mm > 130 hounsfield units	Superficial femoral artery	Not stated	Calcification progression greatest for HD group compared to PD and CKD4 at 12 (p = 0.002) and 24 months (p = 0.01) Determinants of VC progression – gender, age, time averaged ALP, lipid lowering drugs, beta blockers r^2 = 0.64
Raggi et al 2007	HD (131)	55.2	50/50	50.4	Lumbar radiograph. Semi-quantitative 24 point severity score	Thoracic & Abdominal aorta	Not stated	Abdominal but not thoracic aorta calcium scores independently associated with higher PWV (p = 0.004)
Okuni et al 2007	HD (515)	60± 12	59/41	95 ±75	Lumbar radiograph – presence/absence of calcification	Abdominal aorta	56.5%	All cause mortality RR 2.07 (1.21-3.56, p = 0.008) CV mortality RR 2.39 (CI 1.01-5.66, p = 0.048). Mean follow-up 51 ± 17 months.
Sigrist et al 2006	HD (60) PD (28) CKD 4 (46)	60 ±15 61 ±14 60 ±14	70/30 60/40 56/44	36 ±25 34 ± 23	CT - Agatston score system >1mm > 130 hounsfield units	Superficial femoral artery	73% 71% 47%	PWV not associated with calcification score. Calcification score and radial dorsalis PWV r = 0.34 (p < 0.001). Determinants of VC -Age, gender, Ca-P product, DM, r^2 = 0.48.
Chesterton et al 2005	40 HD	62 ±2.1	28/12	40 ± 3.9	CT - Agatston score system >1mm > 130 hounsfield units	Superficial femoral artery	64%	Calcification not correlated with age or HD vintage. Not associated with arterial stiffness. People with VC had significantly lower BRS 3.43±0.38 vs 5.67±0.76 (p = 0.01)
Taniwaki et al 2005	HD 184 DM 483 no DM	 65 ±9 59 ±12	 67/33 59/31	 57.7 ±46.5 139.0 ±91.5	CT – scoring system not stated	Aorta section not stated	Not stated	Aortic calcification of diabetics v non-diabetics: HD vintage <60 months 53.2±22.2 vs 39.2±26.0%, (P<0.001); 60-120 months 63.2±20.5 vs 43.4± 27.9%, P<0.001) Determinants ACI – Age, gender, HD vintage, DM, blood pressure, cholesterol, Ca-P product. R^2 = 0.27
Nitta et al 2004	HD (49)	60±1.6	55/45	115.2 ±9.6	CT – scoring system not stated	Aorta section not stated	Not stated	Calcification index independent predictor of left ventricular mass index along with BP, PWV. r^2 = 0.33

ramifications of altered ventricular morphology are well recognised but the baroreceptor reflex is part of autonomic cardiovascular control and vital in short-term blood pressure regulation.

1.2.3.7 Calcification prevalence and progression

Age attendant calcification of the large capacitive arteries is well documented in older adults (Yu and Blumethal 1963; Post et al. 2007), but it is more severe and more prevalent among people with stage 5 CKD of all ages (Guerin et al. 2001; London et al. 2003; Sigrist et al. 2007; Raggi et al. 2007). Moreover, medial calcification has been observed in middle-aged and young adults with CKD in the absence of traditional CV risk factors (London et al. 2003). People receiving maintenance HD also demonstrate more profound vascular calcification compared to individuals receiving PD and those with stage 4 CKD (Sigrist et al. 2006).

Worryingly, by the time dialysis is commenced at least half of people show some degree of large artery calcification (Guerin et al. 2001; Sigrist et al. 2006) a proportion that increases up to almost three quarters among prevalent HD patients (Chesterton et al. 2005; Sigrist et al. 2006). In comparison, prevalence of large artery calcification among non-uraemic individuals is 37% or less (Kauppila et al. 1997). A longitudinal study confirmed that once dialysis is initiated further vascular calcification ensued with people receiving HD demonstrating a more pronounced degree of progression over two years compared to PD and people with stage 4 CKD (Sigrist et al. 2007).

Presence of medial calcification of the large conduit arteries is also independently predictive of survival in the HD population (table 1.18). Radiographic identification of the presence of calcification of the aorta and pelvic arteries more than doubles the risk of mortality and non-fatal CV events among uraemic individuals over follow-up periods of two to seven years (London et al. 2003; Okuni et al. 2007; Verbeke et al. 2011). Moreover, not only was two year mortality highest among HD participants in a mixed cohort of HD, PD and stage 4 CKD patients but progression of VC determined by CT was also independently predictive of mortality (Sigrist et al. 2007).

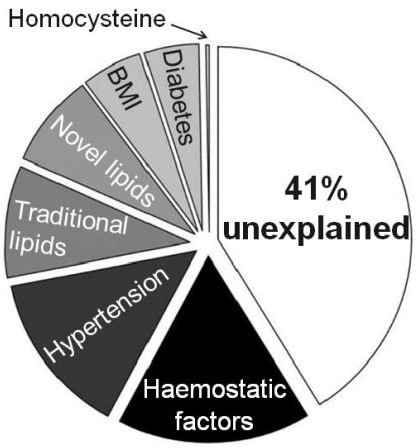
1.2.3.8 Arterial stiffness, physical activity and cardiorespiratory fitness

Although clinical correlates of aortic PWV have been explored the potential behavioural mediators of large artery stiffness have not been investigated in stage 5 CKD. Physical activity (PA) and cardiorespiratory fitness (CRF) are implicated in

survival in mortality in stage 5 CKD (O'Hare et al. 2003; Sietsema et al. 2004; Tentori et al 2010; Matsuzawa et al. 2012), but the mechanism by which higher levels of both mediate improved survival has not been elucidated. Exercise mediated changes in traditional CV risk factors are generally believed to confer better outcomes. However observed improvements are modest, and at least 40% of CVD risk reduction associated with physical activity in healthy individuals (Mora et al. 2007) and cardiac patients (Taylor et al. 2006) remains unexplained (figure 1.14).

Summative improvements in risk factors may be particularly beneficial in disease states, however accumulating evidence indicates that exercise aimed at improving CRF has a direct effect on vascular function. It is believed a certain amount of PA is required to maintain normal vascular health, as inactivity is associated with increased arterial stiffness (Gando et al. 2010a), and endothelial dysfunction (Thijssen et al. 2009; Wang 2005; Green et al. 2004; Suvorava et al. 2004).

Figure 1.14 Relative CVD risk reduction associated with PA (adapted from Thijssen et al. 2010, p. 846).



Currently there is a paucity of research regarding how PA and CRF relate to vascular health in stage 5 CKD. Much of what is known comes from cross-sectional studies in the general population with few data pertaining to clinical populations. Review of the literature shows considerable heterogeneity of arterial stiffness measures employed (tables 1.19 and 1.20). However, there is overwhelming agreement that indices of arterial stiffness of apparently healthy adults are inversely associated with PA levels estimated via accelerometry (Edwards et al. 2012; Aoyagi et al. 2010, Gando et al. 2010a, Kozakova et al. 2007, Sugawara et al. 2006) and self-report questionnaires (van de Laar et al. 2010, Boreham et al 2004).

Table 1.19 Summary of studies exploring the relationship between indices of arterial stiffness and physical activity.

Study	Sample (n)	Age	M/F	Arterial stiffness outcome/s	Findings
Jennersjo et al 2012	Diabetes (327)	60.5 ±3.2	69/31	Aortic PWV	Pedometer steps/day and PWV borderline association r = -0.11 (p = 0.066).
Edwards et al 2012	Diabetes and Obese (548)	18 ±3.3	37/63	Augmentation Index, aortic PWV, brachial artery distensibility	Habitual PA (accelerometer cpm) independently associated with AI and brachial distensibility ($p < 0.05$). Physical activity associated with PWV (correlation not stated) but significant interaction with diabetes status observed.
Van de Laar et al 2010	Healthy (373)	13.1 ±0.8	Not stated	Carotid artery stiffness Longitudinal follow up at age 36	Stiffer carotid arteries significantly associated with less time in self-reported vigorous but not in light-to-moderate intensity PA between adolescence and young adulthood.
Aoyagi et al 2010	Healthy (198)	73.5 ±4.6	45/55	Cardio-femoral PWV Brachio-tibial PWV	Cardio-femoral and delta brachio-tibial velocities significantly lower in participants exceeding 6,600 steps/day and/or > 16 min/day of PA at >3 METs over one year.
Gando et al 2010a	Healthy (538)	49 ± 0.4	32/68	Aortic PWV	Accelerometer estimated moderate PA independently associated with PWV of middle-aged adults (p value not stated). Light PA independently associated with PWV of older adults (p value not stated). Interaction of fitness level in older adults. Light PA and PWV in older unfit subjects ($r = -0.47$, $p < 0.01$). PWV higher in low-light PA level group than high-light PA level group after normalizing for time spent in moderate to vigorous PA ($P < 0.01$).
Kosakova et al 2007	Healthy (432)	43 ± 8	38/62	Carotid artery stiffness Ultrasound	Accelerometer estimated PA (cpm) inversely associated ($r = -0.20$ to -0.25, $p < 0.001$) and independent predictor of carotid stiffness ($p < 0.05$)
Sugawara et al 2006	Healthy (103)	64 ± 7	0/100	Carotid artery stiffness	Accelerometer estimated light, moderate, vigorous PA correlated with carotid stiffness ($r = -0.26$, -0.26, -0.23 respectively, $p < 0.05$). Moderate and vigorous PA independently associated with carotid stiffness ($p < 0.01$).
Boreham et al 2004	Healthy (405)	22.6 ± 1.6	50/50	Aortoiliac PWV Aortodorsalis pedis PWV	Self-reported sports related PA only independently associated aortodorsalis pedis PWV at group level ($p < 0.05$). Leisure time PA independently associated with PWV in males only ($p < 0.05$).

Table 1.20 Summary of studies exploring the relationship between indices of arterial stiffness and cardiorespiratory fitness.

Study	Sample (n)	Age	M/F	Arterial stiffness outcome/s	Findings
Lane et al 2013	Haemodialysis (42)	44.5 ± 5.0	Not stated	Aortic PWV Arterial elastance	Shuttle walk distance and PWV r = -0.39 (p = 0.02); arterial elastance r = -0.42 (p = 0.004). PWV independently associated with walk distance β = -14.68 (p = 0.012)
Jae et al 2010	Metabolic syndrome (867) Healthy (168)	52.0 ± 6.0	100/0	Brachial ankle PWV	VO_2max independently associated with baPWV in men with metabolic syndrome (β = -0.22, p < 0.05) and without (β = -0.12, p < 0.05). No significant difference in baPWV between unfit men without and fit men with metabolic syndrome (p = 0.81)
Gando et al 2010b	Healthy (159)	41.5 ±5.5	0/100	Brachial ankle PWV, Augmentation index	Interaction between age and VO_2peak in arterial stiffness indices (p < 0.01). Older adults with higher fitness had lower arterial stiffness
Boreham et al 2004	Healthy (405)	22.6 ± 1.6	50/50	Aortoiliac PWV Aortodorsalis pedis PWV	VO_2max independently associated with arterial stiffness indices (p < 0.01)
Bonapace et al 2003	Cardiomyopathy (90)	62 ± 11	55/45	Aortic PWV	VO_2max and PWV: group r = -0.39 (p < 0.001); ischaemic r = -0.33 (p = 0.02); non-ischaemic r = -0.55 (p = 0.005). PWV independent predictor of CRF r^2 = 0.34 (p = 0.04)
Ferreira et al 2002	Healthy (351)	36·5 ± 0·6	48/52	Aortic and femoral artery compliance, distensibility.	VO_2max and carotid artery compliance r = 0·19 (p = 0·02); femoral artery compliance r = 0·18 (p = 0·03); distensibility of carotid r = 0·16 (p = 0·047) but not femoral artery.
Tanaka et al 2000	Healthy (151)	47.7 ±1.0	100/0	Carotid artery compliance	VO_{2max} and carotid arterial compliance r = 0.44 (p < 0.005); β stiffness index r = -0.45 (p < 0.005). Arterial compliance of endurance-trained middle-aged and older men 20 - 35% higher than recreationally active and sedentary peers (p < 0.01).
Tanaka et al 1998	Healthy (53)	48.4 ±2.0	0/100	Aortic PWV, Carotid Augmentation index	VO_2max and PWV r = -0.66, carotid AI r = -0.53 (p < 0.001). VO_2max independently associated with PWV and AI (p < 0.001)
Vaitkevicius et al 1993	Healthy (146)	54.3 ±17.0	63/37	Aortic PWV Augmentation Index	Arterial stiffness of endurance trained older adults (54-75years) significantly lower than sedentary peers (AI 36% lower, PWV 26% lower, p < 0.0001) despite similar blood pressures. VO_2max and PWV: men r = 0.34 (p < 0.01); women r = 0.49 (p < 0.01). VO_2max not independently associated with PWV due to age interaction VO_2max and AI: men r = 0.34, (p < 0.001); women r = 0.74 (p < 0.0001). VO_2max independently associated with AI (p = 0.001) along with age.

Habitual PA indicated by accelerometer activity counts is independently associated with arterial stiffness of adolescents (Edwards et al. 2012) and middle-aged adults (Kosakova et al. 2007). In addition, there appears to be a differential effect of PA intensity on arterial stiffness with respect to age. Studies following participants from adolescence to adulthood indicate vigorous activity only is predictive of arterial stiffness among young healthy adults (van de Laar et al. 2010; Boreham et al. 2004) while moderate PA is inversely correlated in samples of middle-aged and older adults (Sugawara et al. 2006; Aoyagi et al. 2010; Gando et al. 2010a). Moreover, subgroup analysis by Gando et al. (2010a) indicated greater amounts of time spent in light PA (< 3 METs) attenuated arterial stiffening of older adults even after adjustment for time spent in moderate and vigorous PA, especially in unfit individuals (Gando et al. 2010a). This may be because CRF declines with advancing age and thus light PA determined by accelerometer is 'harder' in relative terms for older adults compared to younger adults. Interestingly, Jennersjo et al. (2012) found no association between steps/day and aortic PWV of obese individuals but this may be due to underestimation of activity by pedometry in obese populations (Tyo et al. 2011).

A moderate correlation between a surrogate measure of aerobic fitness determined via a shuttle walk test and aortic PWV has been observed in a sample of maintenance HD patients (Lane et al. 2013). This is in agreement with associations observed in samples of apparently healthy middle-aged adults (Tanaka et al. 2000) and older adults with dilated cardiomyopathy (Bonapace et al. 2003). Several studies have shown CPET measured CRF is independently associated with large artery stiffness of non-uraemic individuals (Vaitkevicius et al. 1993; Tanaka et al. 1998; Boreham et al. 2004; Jae et al. 2010). Moreover endurance trained seniors with higher CRF demonstrate attenuated arterial stiffness compared to sedentary peers despite similar blood pressures (Tanaka et al. 1998; Gando et al. 2010b). Endothelial function, which represents the functional component of arterial stiffness is also strongly associated with CRF in non-uraemic adults (Palmieri et al. 2005).

Boreham et al. (2004) contend that higher CRF mediates the relationship between PA and arterial stiffness in young adults. However, the authors employed self-reported PA, which is arguably susceptible to greater measurement exposure error compared to CPET measured CRF. Consequently, lower accuracy and reliability of subjectively estimated PA may have adversely affected the strength of association with arterial stiffness in multivariable analysis. The work of Chen et al. (1998)

indicates ventricular systolic and aortic function form an important coupling, which is physiologically matched for optimum cardiac efficiency. Stiffer vessel walls adversely affect cardiac function by increasing aortic impedance to stroke volume from the left ventricle (Shibata et al. 2008) resulting in a stiffer ventricle in people with CKD (Edwards et al. 2008) and invariably leading to LVH (Foley et al. 1998). Aortic stiffness is independently predictive of VO_2peak in people with dilated cardiomyopathy (Bonapace et al. 2003) and a physical performance estimate of CRF in a sample of maintenance HD patients (Lane et al. 2013). Taken together it appears CRF is more likely an expression of increased aortic stiffness rather than a mediator in stage 5 CKD.

Given the number of studies showing arterial stiffness is associated with PA and CRF it is of great concern that the HD population is characterised by high prevalence of low levels of both (O'Hare et al. 2003; Tentori et al. 2010; Painter et al 2011; Parsons and King-van Vlack 2009). By extension, observed associations between indices of large artery stiffness and fitness level and PA may explain why the latter are predictive of survival in the HD population. However, whether habitual PA mediates improved survival in stage 5 CKD has not been explored. Research in this area is warranted to provide additional support for KDOQI recommendations pertaining to activity counseling for management of CVD risk in this population.

1.2.3.9 Summary and research questions

Although arterial stiffening is a pathophysiological process that is driven by advancing age (O'Rourke and Hashimoto 2007), accelerated vascular aging is a putative phenotype of stage 5 CKD (London et al. 2011, Pannier et al. 2005). Arterial stiffening observed in uraemia may be viewed as the manifestation of age associated decline in extracellular composition of the vessel wall, chronic elevation of central pressure, bone demineralization, and reduced glycaemic control. Progressive vascular calcification and increased arterial stiffness have been observed with greater dialysis duration in prospective studies (Sigrist et al. 2007; Avramovski et al. 2013), however, HD vintage has not been identified as a risk factor. Importantly, habitual PA and higher CRF are implicated in survival of maintenance HD patients (Sietsema et al. 2004; Tentori et al. 2010; Matsuzawa et al. 2012). It is possible the relationship between higher CRF and PA levels and lower mortality risk in CKD may be mediated via the formers' influence on a CV intermediate endpoint such as arterial stiffness. Aortic PWV and AI have prognostic

utility in stage 5 CKD (London et al. 2001a; Blacher et al. 2003; Pannier et al. 2005; Verbeke et al. 2011) and are increasingly being adopted as intermediate endpoints to assess effectiveness of intervention studies targeting CV health. Standardisation of the most appropriate arterial stiffness outcome is necessary to enable meaningful synthesis of findings from existing and future studies.

What is the relative contribution of habitual physical activity to indices of central arterial stiffness of people receiving maintenance haemodialysis?

Which measure of arterial stiffness is most appropriate for monitoring vascular health of maintenance haemodialysis patients?

Given that progressive vascular calcification, greater prevalence of LVH and higher mortality risk are observed with longer dialysis duration, is HD vintage a predictor of arterial stiffness in stage 5 CKD?

Chapter 2: General methods

2.1 Recruitment

2.1.1 Ethical approval

The studies undertaken conformed to the Declaration of Helsinki and were approved by the West of Scotland Research Ethics Committee (appendix I a), research and development department at Monklands Hospital, Airdrie (appendix I b), and Queen Margaret University, Edinburgh. Potential participants who registered interest in the studies were provided with a study information sheet (appendix I c) with a Flesch Reading Ease score (Flesch 1948) equating to a reading age for someone 13 to 15 years old (score = 63.3). People who agreed to participate were again informed of the assessment methods and procedure verbally and allowed a seven day 'cool-off' period. Written informed consent (appendix 1 d) was obtained from participants prior to study participation.

2.1.2 Participants

A convenience sample was recruited from men and women undergoing maintenance haemodialysis therapy (thrice weekly) for the treatment of stage 5 chronic kidney disease (CKD). Potential participants were recruited from a single renal dialysis unit at Monklands Hospital, and were approached initially by the medical team responsible for their care. Pamphlets advertising the study (appendix 1 e) were distributed among people undergoing maintenance HD by nursing staff at the renal unit. A recruitment pack comprising a study information sheet, consent and participant contact form was given to those who subsequently registered interest. Participants had to be aged 18 years or over (no upper age limit) and be able to ambulate a minimum of 10 metres. Ambulation with a walking aid was acceptable. People with dementia or severe cognitive impairment were excluded from participation. Treating physician approval prior to taking part in the study was mandatory to ensure all participants were medically stable for physical performance assessments.

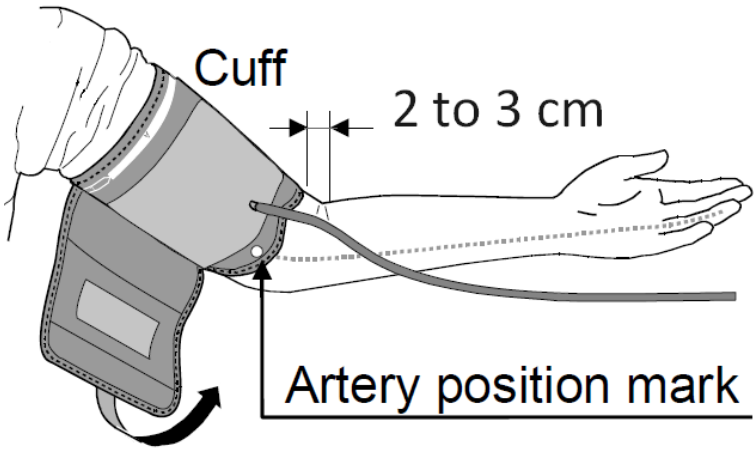
2.2 Measurement of vascular indices of health

2.2.1 Blood pressure

Brachial blood pressure (BP) was measured using an AND Model UA-767 digital oscillometric blood pressure monitor (A&D instruments Ltd, Oxfordshire), which has

documented clinically acceptable validity and reliability (Rogoza et al. 2000). Blood pressure and resting heart rate were measured following 15 minutes of complete rest (Appel et al. 2002; Jones et al. 2003) in a quiet room. Participants were positioned semi-recumbent (40° head up). The width of the monitor cuff bladder was approximately 40% of the arm circumference and was placed on the bare non-arteriovenous fistula arm 2 - 3 cm from the elbow crease as per the manufacturer's instructions (figure 2.1).

Figure 2.1 Blood pressure cuff position (A&D Instruments Ltd, [undated], p. 12).



Shirt sleeves were rolled above the cuff so as not to constrict the arm. The arm from which BP was measured was supported on a pillow at the same level as the heart (Appel et al. 2002; Jones et al. 2003). Blood pressure (mm Hg) and resting heart rate (beats/min) was determined from an average of three measures with a two minute inter-measurement interval (Jones et al. 2003).

2.2.2 Aortic pulse wave velocity

Carotid femoral pulse wave velocity (PWV) was measured using a Vicorder (Skidmore Medical Ltd, Bristol, UK). Apparatus calibration was undertaken prior to the study using a manometer as described in section 1.7 of the Vicorder manual (Skidmore Medical Ltd 2009). Participants were positioned according to Vicorder protocol recommendations: supine with head up (30° from horizontal plane), and with a small towel roll under the knees for comfort as required. Table 2.1 outlines standardisation of participant testing conditions.

Table 2.1 Standardisation of participant assessment conditions (Laurent et al. 2006).

Confounding factor	In practice
Room temperature	Controlled environment kept at 22 ± 1°C.
Vascular tone	At least 10 min rest in recumbent position prior to measurement.
Time of the day	Similar time of the day for repeated measurements (± 1 hour).
Smoking, eating	Participants refrain from smoking, ingesting food and beverages containing caffeine at least 3 hours prior to assessment.
Alcohol	Refrain from drinking alcohol 10 hours before assessment.
Speaking, sleeping	Participants may neither speak nor sleep during measurement
Position	Supine position (30º head up as per Vicorder protocol manual).
White coat effect	Influence on blood pressure and pressure-dependent stiffness.
Cardiac arrhythmia	Be aware of possible disturbance.

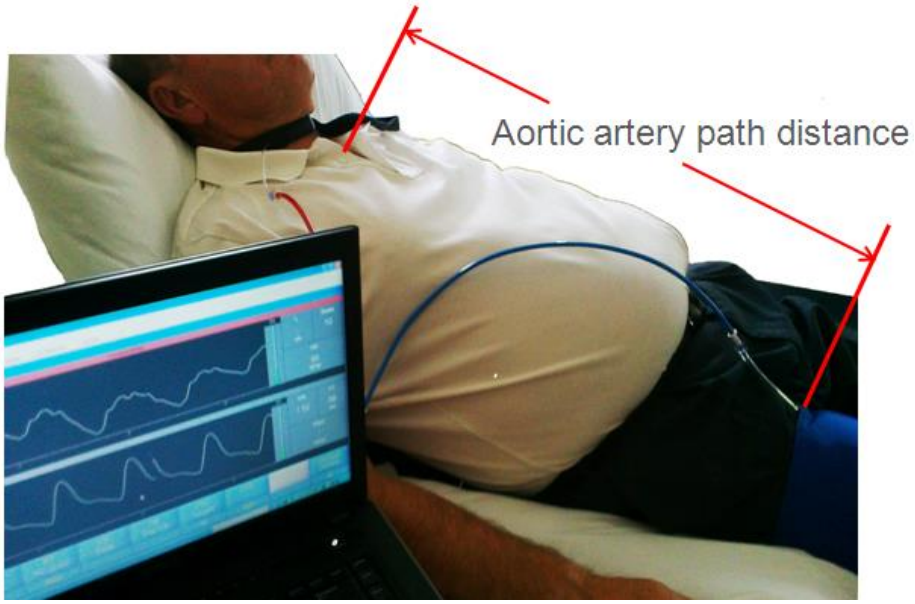
PWV measurement required the placement of two pressure cuffs, one over the carotid artery and the other over the femoral artery on the ipsilateral side. The carotid artery was palpated by positioning one or two fingers between the larynx and the anterior border of the sternocleidomastoid muscle at the level of the cricoid cartilage. In palpating the pulse, the degree of pressure applied to the artery was varied until maximum pulsation was appreciated (Felner 1990). The proximal cuff was then fitted with the transducer over the palpated carotid site (figures 2.2 and 2.3).

Figure 2.2 Carotid pressure cuff placement (Skidmore Medical Ltd, 2009, p. 49).

Figure 2.3 Femoral pressure cuff placement (Skidmore Medical Ltd, 2009, p. 49).

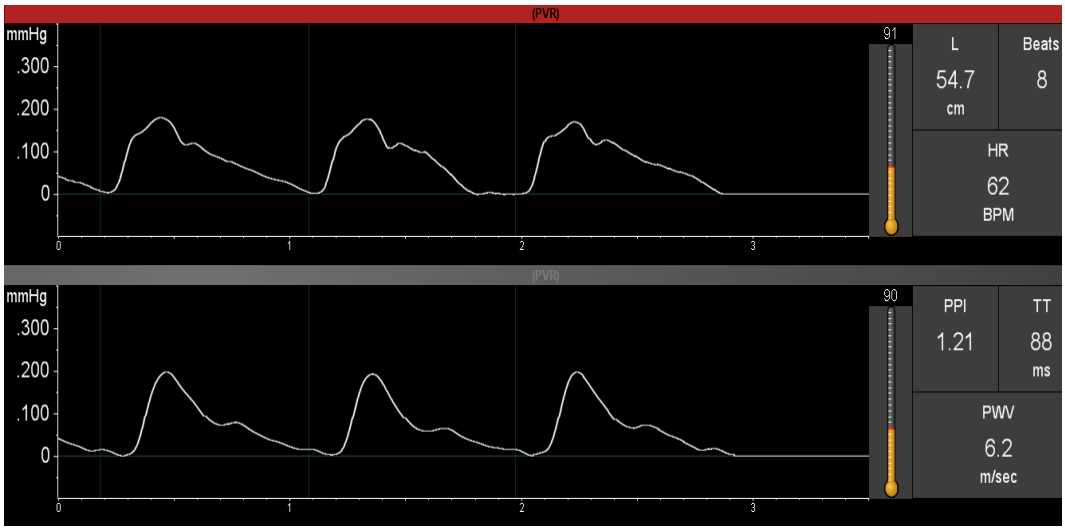
The femoral pressure cuff was placed around the right thigh as high as practicable (figure 2.3). The distance from the suprasternal notch to the top of the femoral cuff was measured to represent the aortic artery path in accordance with Vicorder manual instructions (figure 2.4). Obesity or large breast size can result in inaccurate aortic arterial path measurement consequently influencing the absolute value of PWV (Laurent et al. 2006). To nullify the effect of body contours, the distance from the suprasternal notch to the femoral cuff was therefore measured with an anthropometer (Huybrechts et al. 2011).

Figure 2.4 Participant PWV assessment position and Vicorder analysis screen.



Parameters required for PWV were entered (systolic and diastolic BP, arterial path distance) as per the Vicorder protocol manual, section 6.2 (Skidmore Medical Ltd, 2009). Participants were habituated to pressure cuff inflation and then allowed to rest for 15 minutes. PWV calculations are displayed after two complete screens of continuous pulse wave monitoring. The Vicorder calculates a rolling average of PWV over subsequent cardiac cycles (figure 2.5). Instantaneous measurements of an oscillating system are influenced by preceding wave forms, therefore PWV values were recorded after a 10 second period equating to approximately 15 cycles (Frimodt-Moller et al. 2008). Measures were repeated in triplicate with a two minute interval (Savage et al. 2002). The mean PWV value was reported with measures outside two standard deviations discarded from analysis (Hickson et al. 2009).

Figure 2.5 Example of participant PWV measurement in process.



2.2.3 Augmentation index

Augmentation Index (AI) was measured using the same Vicorder unit employed for PWV measurement. Participant position and standardisation of measurement conditions were the same as those for PWV. As with PWV measurement, participants rested recumbent for 15 minutes prior to assessment to reduce potential confounding effects of PA induced changes in vascular tone (Dawson et al. 2009) Parameters required for pulse wave analysis screen were entered (systolic and diastolic BP, analysis site) as per the Vicorder protocol manual, section 7.1 (Skidmore Medical Ltd, 2009).

A pressure cuff was placed around the non-arteriovenous fistula arm 2 - 3 cm above the elbow crease (figure 2.6). Once in position, the cuff was inflated and the Vicorder commenced AI measurement. The Vicorder starts displaying AI measures continuously after optimum cuff pressure is reached (figure 2.7). Vicorder calculated mean AI was recorded after a 10 second period (Frimodt-Moller et al. 2008) and repeated in triplicate with a two minute interval in between (Savage et al. 2002). As with PWV measurement, mean AI was reported with measures outside two standard deviations discarded from analysis (Hickson et al. 2009).

Figure 2.6 Vicorder cuff position for Augmentation Index measurement.

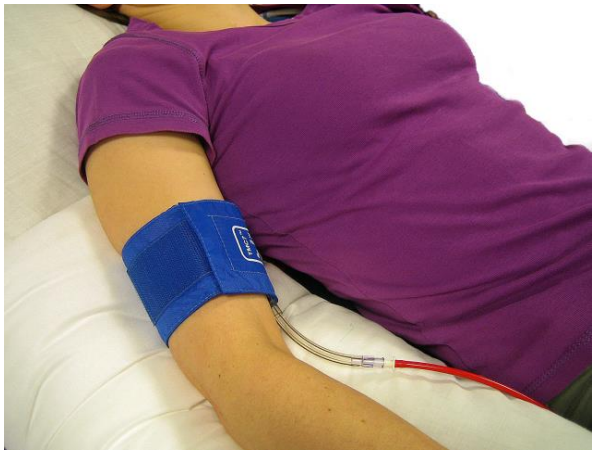
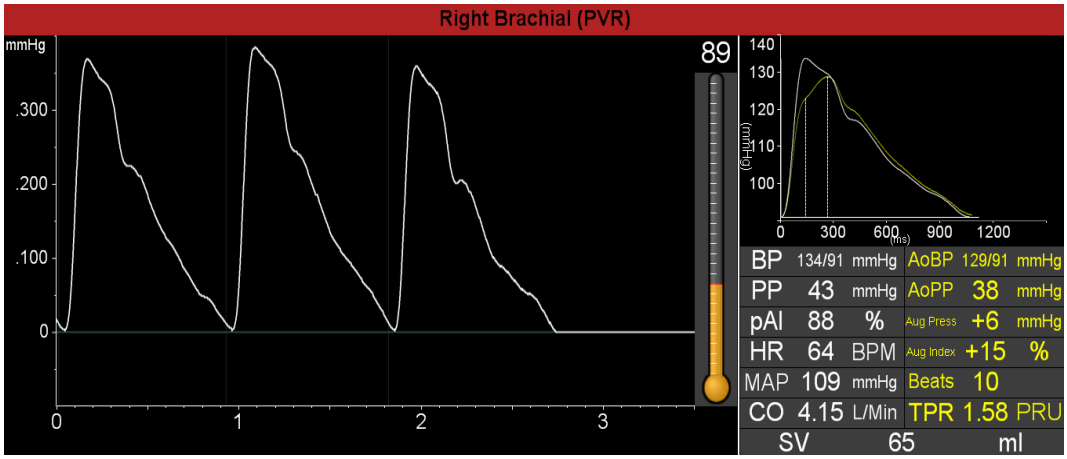


Figure 2.7 Example of participant augmentation index measurement.



Measures of vascular stiffness (PWV and AI) were taken on a non-dialysis day to minimise the influence of dialysis mediated volume alterations on waveform analysis (Covic et al. 2000). Medications such as those used to manage hypertension, congestive heart failure, cholesterol, diabetes and advanced glycation end products are known to influence measurement of arterial stiffness (Shimamoto and Shimamoto 1995; Kelly et al. 2001; Agata et al. 2004; Laurent et al. 2006, Williams et al. 2006). However, asking participants to abstain from medications the day before assessment was not indicated for reasons of safe medical management. In addition, half-life of vasoactive medications can often be 12 hours or more (Kelly and O'Malley 1990). Therefore, participants' medications were recorded to assist discussion of results.

2.3 Assessment of physical function by physical performance tests

2.3.1 Hand-grip strength: apparatus, set up and procedure

Apparatus for the grip strength assessment included a JAMAR hand dynamometer (Lafayette Instrument Company®, Lafayette USA) a chair with arm rests and a digital stopwatch. Prior to commencing the test the hand-grip dynamometer was adjusted to the desired hand spacing: the handle base rested on the first metacarpal (heel of palm), while the handle rested midway along the four fingers (Mathiowetz et al. 1984; Roberts et al. 2011). The participant sat with their shoulder adducted against the side of their body elbow flexed at 90°. The dynamometer was held in the hand to be tested with the forearm resting on the chair arm in the neutral position (0° pronation), and wrist between 0° and 30° extension with 0° to 15° ulnar deviation (figure 2.8) (Mathiowetz et al. 1984; Roberts et al. 2011).

Figure 2.8 Standardised grip strength test position.

Explanation was provided to the participant regarding the grip strength assessment sequence. A script standardised for the grip strength test was as follows: “Please sit with your back against the chair and your arm to be tested resting on the arm rest. Keep your elbow bent at 90° and in at your side with your hand forward of the edge of the armrest. During the test I would like you to squeeze the handle like this”. A grip test was demonstrated and the dynamometer then passed to the participant. “Hold the handle with the indicator dial facing slightly up and away from you. I will ask you to squeeze the handle for five seconds when I say squeeze. During that time I will encourage you to give a maximum effort until I ask you to stop. Please do not hold your breath during the test, instead breath out”.

Participant understanding of the test instructions was checked by asking them to repeat the instructions. The peak-hold needle on the dynamometer was reset to zero, and the start of the grip test was cued with: “Are you ready? Squeeze!” While the participant was squeezing the dynamometer handgrip they were strongly encouraged to give a maximum effort with the following script “squeeze as hard as you can,... harder,... harder,...relax” (Mathiowetz et al. 1984).

Grip strength testing of the arterio-venous fistula arm can be carried out as long as the fistula is well healed (Koufaki and Kouidi 2010). Three attempts with each hand were performed with 30 - 45 seconds of recovery in between each attempt. Grip strength was recorded to the nearest kg of force and the peak-hold needle was reset to zero each time. The best performance of the six efforts was recorded for data analysis (Roberts et al. 2011).

2.3.2 Sit-to-stand five test – apparatus, set up and procedure

Apparatus for the sit-to-stand five test (STS5) included a height adjustable straight-backed chair with rubberised leg ends to prevent slippage. The chair had no armrests or seating cushion, and approximate seating area dimensions were: height 45 cm; width 50 cm; depth 40 cm (Csuka and McCarty 1985). The chair back was placed against the wall to prevent movement and the participant was seated in the middle of the chair, with back straight and feet approximately shoulder width apart. To ensure angular and linear work was constant between participants, the height of the chair was adjusted so that knee flexion angle was 100 - 105° and the ankles were positioned in 10° dorsiflexion (Cheng et al. 1998). If required, one foot was permitted to be placed slightly ahead of the other to aid balance. Arms were folded across the front of the chest and the test was performed either barefooted, or in low-heeled shoes.

Explanation was provided to the participant regarding the sequence and the outcome of the test. Participants were instructed to look straight ahead and to stand up with their weight evenly distributed between both feet. The participant was reminded that they must come to a full stand position with knees straight and that their performance would be timed by the tester (figure 2.9).

Figure 2.9 Sit-to-stand five test.

The STS5 protocol script was as follows. “When I say ‘go’ you may stand up to a full standing position and sit down again as quickly as you can without using your arms. Repeat this movement four more times as quickly as you are able. The test ends when you sit for the fifth and final time. At this point please remain sitting. Timing will start when I say ‘go’ and finish when you sit down for the fifth and final time”.

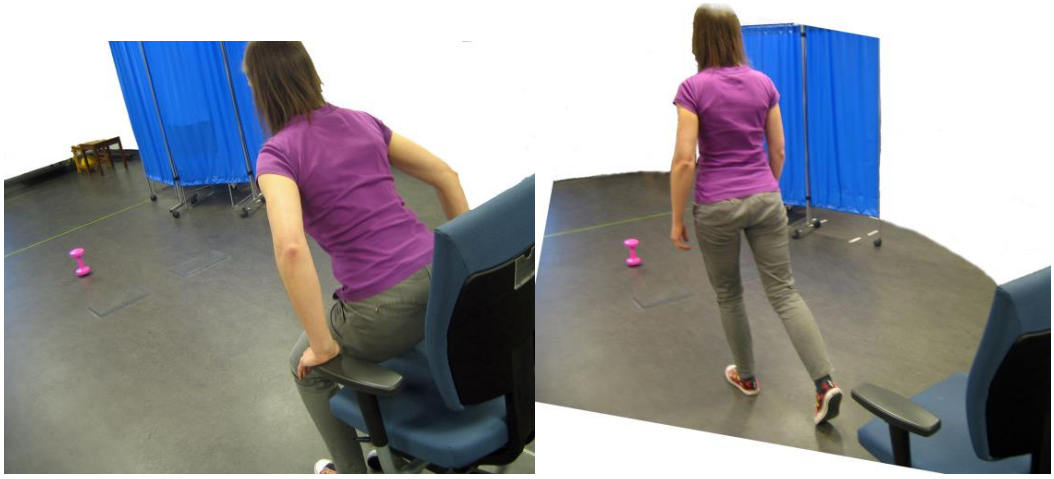
Participant understanding of the test instructions was checked, and the tester subsequently cued the start of the test with “ready, set, go”. Timing of the STS5 commenced on the “go” command and concluded as soon as the participant sat down after the fifth and final stand (Schaubert and Bohannon 2005). Time taken to complete the STS5 was recorded with a digital stopwatch to the nearest tenth of a second. The STS5 test was repeated twice, following the same procedure with a one minute rest interval in between tests. The last or best performance was recorded for data analysis (Schaubert and Bohannon 2005).

2.3.3 Timed up-and-go test – apparatus, set up and procedure

Apparatus for the timed up-and-go (TUAG) test included a chair with arms (approximate seat height 46 cm with arm height 65 cm). A marker cone was placed three metres from the armchair marking the end of the walking course. Prior to the test the walking surface was inspected to ensure it was free from slip and trip hazards. A digital stopwatch was used to measure the time taken by the participant to stand up, walk three metres, turn level with the marker cone, and return to sit down in the chair again (Podsiadlo and Richardson 1991). Participants completed the TUAG independently and were allowed to use a walking aid if required.

Explanation was provided to the participant regarding the sequence and the outcome of the test. The timed up-and-go test script was as follows: “Please sit with your back against the chair with your arms resting on the arm rest. If you require a walking aid you may keep this close at hand but please do not hold the aid prior to the test. When I say go, you may stand up, walk to the cone on the floor, when you are level with the cone, turn and walk back to the chair and sit down. Walk at a safe and comfortable walking speed, but do not run. Timing will start when I say ‘go’ and finish once you have returned and sat down” (figure 2.10).

Figure 2.10 Timed up-and-go test procedure



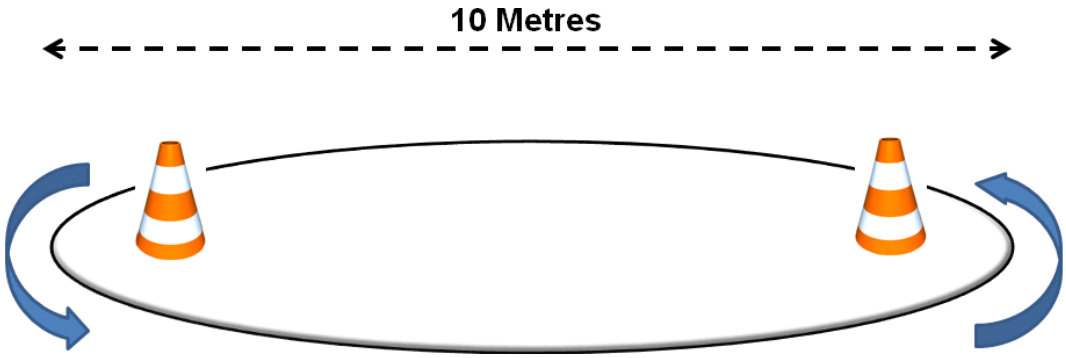
Participant understanding of the test instructions was checked by asking them to repeat the instructions and they were then familiarised with the TUAG by walking through the test (Shumway-Cook et al. 2000). The tester subsequently cued the start of the test with “ready, set, go”. Timing of the TUAG was commenced on the “go” command and concluded as soon as the participant returned from the marker cone and their buttocks contacted the seat. Test time was recorded to the nearest tenth of a second. The participant repeated the test after a 15 - 30 second rest and the second or best performance was recorded for data analysis. Whether the participant required a mobility aid was also recorded (Shumway-Cook et al. 2000).

2.3.4 Incremental Shuttle Walk Test – apparatus, set up and procedure

A proxy measure of cardiorespiratory fitness (CRF) was determined by physical performance during an incremental shuttle walk test (ISWT) (Singh et al. 1992). The original test contained 12 levels (1020 m). However, as the study population might include younger, active individuals, the modified shuttle walk test, which has three

more levels (1500m) allowing participants to run was used to reduce possible ceiling effect threats (Bradley et al. 1999). Apparatus for the modified shuttle walk test included: two marker cones; portable CD stereo system; Modified Incremental Shuttle Walk CD (Leicester Hospital, Leicester UK); Polar heart rate monitor (Polar Electro oy Kempele, Finland). The ISWT was performed in a low use section of corridor in the renal unit with sufficient floor area for a 10 metre long walking course, allowing adequate space to perform turns around the marker cones (Singh et al. 1992). The walking surface was inspected prior to use to ensure it was flat and free from slip and trip hazards. A 10 metre walking course was measured and marked with the marker cones placed 0.5 metres from each end to avoid the need for abrupt changes in direction (figure 2.11).

Figure 2.11 Marked 10 metre course for ISWT.

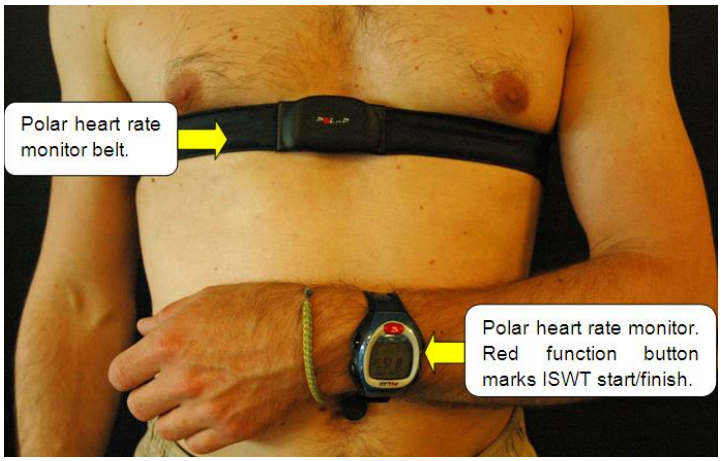


2.3.4.1 Standardisation of participant pre-test conditions

In order to optimise test validity, an attempt was made to control factors known to influence physiological response by informing participants how to prepare for the test in a pre-appointment letter. To minimise the effects of diet induced thermogenesis participants were asked to refrain from ingesting food and beverages containing caffeine in the three hours prior to assessment as well as abstain from ingesting alcohol in the 10 hours prior to the measurement session (ACSM 2010; McArdle et al. 2010). Participants were also asked to avoid strenuous forms of activity during the 24 hours prior to the test (McArdle et al. 2010) to minimise physiological effects from intense PA on the ISWT. For participant safety and later data analysis, heart rate response was monitored throughout the ISWT using a Polar heart rate monitor (Polar Electro oy Kempele, Finland). The monitor belt was

positioned as pictured in figure 2.12. Atomized spray was placed on the monitor belt contact points to assist skin conductivity of heart rate signal.

Figure 2.12 Wear position of Polar heart rate monitor belt.



2.3.4.2 Test Procedure

Track one of the ISWT CD provided participants with a standardised script explaining the sequence of the test and outcome. The CD instructed participants to: "Walk at a steady pace aiming to turn around the cone at one end of the course when you hear the signal.... You should continue to walk around the cones until you feel that you are unable to maintain the required speed." A practice walk is recommended for the test as a learning effect has been identified (Singh et al. 1994; Morales et al. 1999; Dyer et al. 2011). In order to balance this consideration with time constraints participants were allowed to walk the first two levels in order to familiarise themselves with the course and pacing strategy. Prior to starting the ISWT participants were familiarised with the BORG rating of perceived exertion scale (Borg 1998) using a uniform script with the scale (appendix II). Participant rating of perceived exertion and reason for ISWT cessation was recorded at the test endpoint.

The start of the ISWT was signalled by a triple bleep and thereafter the CD emitted a bleep at regular intervals to regulate the time allowed for each shuttle. Participants were reminded that they should aim to match their walking pace so that they turned round the marker cone at each end of the course with the sound of the bleep. Each level of the ISWT lasted for one minute. The start of the next level was indicated by a triple beep and the walking speed was incrementally increased (0.17 m/s) by the addition of an extra shuttle.

2.3.4.3 Incremental Shuttle Walk test endpoint

Endpoint of the test was determined by the participant, for example when they became too breathless to maintain the required walking speed (Singh et al. 1994). Indication for the tester to discontinue the assessment was failure of the participant to complete the shuttle in the time allowed. If the participant was less than 0.5 metres from the cone when the bleep sounded they were given another 10 metre length to recover the 'lost' distance. If the participant was unable to do this then the test was discontinued. A cool-down period was undertaken following the test, during which the participant walked slowly around the course four more times to avoid possible hypotensive syncopal attacks associated with abrupt cessation of exercise (Friedwald and Spence 1990). Monitoring of participants continued until heart rate and blood pressure indices had returned to pre-test levels (ACSM 2010). To ensure participant safety the following additional criteria indicating the endpoint of a physical performance test (ACSM 2010) were adhered to:

- Onset of angina or angina like symptoms.
- Shortness of breath, wheezing, leg cramps, or claudication.
- Signs of poor perfusion: light headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin.
- Failure of heart rate to increase with increased exercise intensity.
- Participant request to stop test.
- Physical or verbal manifestations of severe fatigue.
- Failure of the testing equipment.

2.3.4.4 Scoring and reporting the Shuttle Walk outcomes

Shuttle walk test distance was derived from the number of completed levels and shuttles was recorded. For example if the participant finished after the 3rd completed shuttle of the 7th level this was recorded as:

6 completed levels + 3 completed shuttles

Distance walked by the participant was calculated from the ISWT manual:

6 completed levels = 33 shuttle lengths (33 x 10m)

3 completed shuttles = 3 shuttle lengths (3 x 10m)

Distance walked = 360 metres

The outcome of the ISWT was reported in metres. A CRF value (ml/kg/min) was also calculated from ISWT performance using the peak walking velocity achieved during the test and the following ACSM (2000) equation. A fitness value in metabolic equivalents (METs) was subsequently derived by dividing this value by 3.5 (McArdle et al. 2010).

Walking: VO_2 = (0.1 (walk velocity) + 1.8 (walk velocity) (fractional grade) + 3.5

Running: VO_2 = (0.2 (walk velocity) + 0.9 (walk velocity) (fractional grade) + 3.5

2.4 Self-reported/subjective physical function outcomes

2.4.1 Duke Activity Status Index

A subjective indication of physical function was obtained using the Duke activity status index (DASI) (Hlatky et al. 1989). The questionnaire was administered to participants during their non-dialysis day assessment visit. Participants were asked to read the questionnaire instructions on the first side before filling out the DASI questionnaire on the reverse side of the form. They were then asked to answer each item as honestly as possible indicating yes or no for each item with a tick or cross. The DASI questionnaire (appendix III) contains 12 items from simple activities of daily living to participation in more physically demanding leisure time pursuits. The scores for each item are weighted according to their approximate physiological cost. Completed DASI questionnaires were entered on a spreadsheet and a score out of 58.2 was derived. A higher score indicated a better level of functional capacity to perform activities of daily living. If the completed questionnaire contained a 'missed item', a value was imputed based on a ratio of completed items using the equation below (Field 2013). If there were more than two missed items the questionnaire was ruled invalid and not used for data analysis.

Final score = (Initial score/(12-number of missed items)) x 12

A cardiorespiratory fitness (CRF) value was also derived from participant scores using the following formula developed by the authors of the DASI (Hlatky et al. 1989): **VO_2 (ml/kg/min) = (DASI score x 0.43) + 9.6**

2.4.2 Kidney Disease Quality of Life – Short Form™

The UK English (version 1.2) Kidney Disease and Quality of Life Short Form™ (KDQOL-SF™) was used to measure perceived quality of life. The instrument was developed by the RAND corporation (Hays et al. 1995) and contains the Medical Outcomes Short Form 36 (MOS-SF 36) at its core. The MOS-SF 36 contains eight

domains covering: physical function; physical role limitation; emotional role limitation; vitality (fatigue/energy); emotional function; social function; body pain; perception of general health. Twelve domains relating specifically to participants experience of chronic kidney disease stage 5 also comprise the KDQOL-SF which include: symptoms; burden and effect of kidney disease; work status; sleep; sexual function; cognitive function; work status; social interaction and support; staff encouragement; satisfaction with care; general health. This self-administered questionnaire was given to participants during a scheduled HD therapy session (the third dialysis session of the week) following an inter-dialytic period of one day. Completion instructions for the questionnaire were situated on pages two and three of the form. Sight impaired participants were allowed assistance from a family member to complete the KDQOL-SF.

Once completed participants placed the questionnaire in a sealed envelope and returned it to the nursing staff for collection. Answers from the completed questionnaires were entered into a spreadsheet containing the KDQOL-SF™ Version 1.3 scoring programme obtained online from www.rand.org. The spreadsheet subsequently aggregated scores for the different domains of the KDQOL-SF™ and transformed them linearly to a 0 - 100 range. Domain scores were an average of all items in the subscale answered by the participant with missing items not taken into account (Hays et al. 1995). Higher scores indicated better health related quality of life status. Output also included two summary scores based on weighted results from the different domains: the physical component summary score (PCS) and mental component summary score (MCS). The PCS was employed as a measure of self-reported physical function.

2.4.3 Leicester Uraemic Symptom Scale

The Leicester Uraemic Symptom Scale (LUSS) (Wright et al. 1994) was employed to reflect participant perception of the number, frequency and intrusiveness of uraemic symptoms experienced. The LUSS was developed in the UK and therefore expected to have greater cultural validity. Symptom number, frequency and severity are reported to be greater following a period of two non-dialysis days (Nelson-Danquah et al. 2010). The LUSS was administered during the second HD therapy session of the week following one non-dialysis day to reflect a more stable period of symptom experience. Three scores were obtained from the 10 item LUSS (appendix IV). The number of uraemic symptoms experienced (LUSS 1) was indicated by a

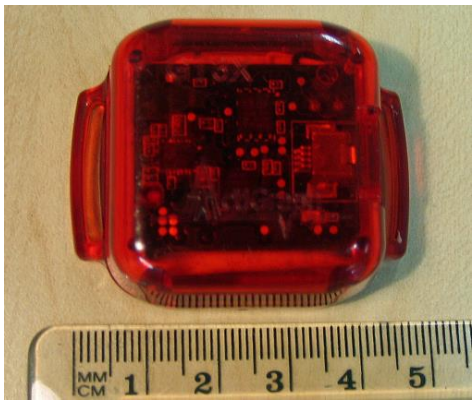
simple additive score (range 0 - 10). In part one of the LUSS, frequency of each symptom (LUSS 2) was rated on a five point Likert scale (0 = never to 4 = everyday) and a summative score was derived (range 0 - 40). Symptom intrusiveness (LUSS 3) was rated in part two, again on a five point Likert scale (0 = not at all intrusive to 4 = extremely intrusive). An overall symptom burden score was derived (LUSS 4) by adding scores for symptom frequency and burden together. Higher scores indicated greater condition related symptom burden.

2.5 Assessment of physical activity

2.5.1 Actigraph Accelerometer

The Actigraph GT3X (Actigraph Corp, Pensacola, FL) is a triaxial accelerometer (figure 2.13) that has been commercially available since 2009. The GT3X is a solid-state accelerometer, which uses an integrated micromachined monolithic integrated circuit chip (polysilicon) to detect body acceleration. An advantage of the GT3X over earlier uniaxial Actigraph monitors (7164 and GT1M) is that it is able to measure movement in three planes via a triaxial capacitive micromechanical system (John and Freedson 2012). The sensor is suspended by springs over the surface of silicon wafer and provides a resistance against acceleration forces (Analog Devices 2007). Body accelerations within a range of 0.05 - 2.0g are recorded in three individual orthogonal planes of movement (vertical, mediolateral, anteroposterior) and the raw data are then converted into activity counts. Higher activity counts result from greater or more frequent accelerations.

Figure. 2.13 Actigraph GT3X accelerometer (Actigraph Corp, Pensacola, FL).



The device also filters the raw data so that only movements within a given frequency (0.25 - 2.5Hz) are recorded. The Actigraph samples at a rate of 30 Hz and data can

be recorded over epochs of varying lengths from upwards of one second. The GT3x has an inclinometer function, enabling detection of different body postures, however, classification accuracy is fair to good (AUC = 0.60.6 - 66.7) (Carr and Mahar 2012), with standing periods often misclassified as sitting (McMahon and Brychta 2010). Therefore, inclinometer output was not reported.

The GT3X monitors were recharged and initialised using a laptop PC. During initialisation all monitor functions were enabled so that the GT3X could record movement in both uniaxial and triaxial formats, as well as step counts. The GT3X was initialised to capture data over 15 second epochs to improve detection of intermittent bouts of moderate to vigorous activity (McClain et al. 2008) and was programmed to commence data collection following the participant's physical assessment. One waist mounted Actigraph monitor was used to monitor a participant's habitual physical activity.

Figure 2.14 Wear position of Actigraph GT3X monitor.

2.5.2 Actigraph GT3X wear protocol

Participants were given uniform scripted instructions on wear time and positioning of the GT3X both verbally and in a leaflet (appendix V a). The GT3X may be worn on the wrist, however there is a risk of increased participant reactivity and tampering with the monitor in this position (Trost et al. 1998). Recommended accelerometer placement is as close as possible to the body's centre of mass (Puyau et al. 2002), with monitor placement on the lower back or the hip providing comparable levels of output (Trost et al. 2005). Haemodialysis patients have an additional 12 to 15 hours spent seated or reclined imposed upon them, therefore comfort and consequent wear compliance were also considerations. The GT3X was positioned on the non-

dominant hip in the mid axillary line just above the anterior superior iliac spine (Figure 2.14) (Yngve et al. 2003; Trost et al. 2005; Lyden et al. 2011). The GT3X was worn during waking hours for eight days following the participant's physical assessment. The monitor was to be removed for bathing, showering, swimming and replaced again straight afterwards. Participants were also asked to note times when the monitor was put on and taken off using the wear log on the back of the monitor wear instruction sheet (appendix V b). The GT3X was collected from the participant on the eighth day after their physical assessment during a routine hospital visit for HD therapy. Data were downloaded from the monitor using proprietary Actilife software (version 5.8.3) onto a laptop PC.

2.5.3 Actigraph GT3X data cleaning

Once downloaded from the GT3X each participant's accelerometry data collected over nine days was cleaned prior to analysis. The first day of wear (assessment day) was deemed a practice day and not included for analysis due to possible increased participant reactivity. The last day of data when the monitor was collected was also removed. The first stage of the data cleaning process involved identification of spurious data. A threshold of 20,000 counts/min is deemed the upper limit of physical activity (PA) that is physiologically possible (Colley et al. 2010). An activity count above this threshold is believed to be biologically implausible and suggests an error with the activity monitor. Minute-by-minute visual inspection of participant GT3X PA files was performed and accelerometry data >20,000 counts/min were discarded from analysis.

2.5.4 Determination of Actigraph GT3X wear time

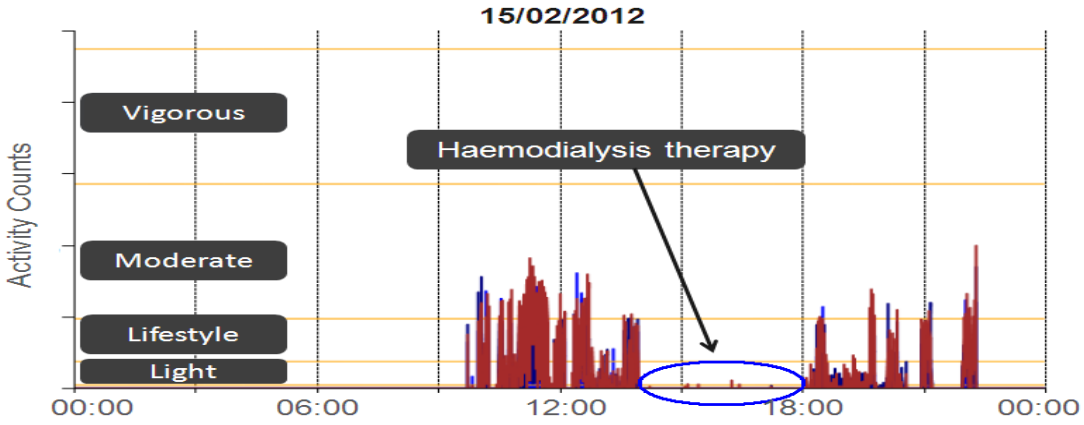
Actigraph monitor wear time was determined using the Actilife 5 software. Wear time assessment is regarded as key to determining participant compliance and whether data should be used for analysis. Monitor non-wear time was determined from a predefined number of zero counts per minute (cpm) in the accelerometery data. Wear time is reported to vary with non-wear time definition. For example, shorter periods of consecutive zeroes to denote non-wear time can result in fewer hours of wear time (Evenson and Terry 2009). Importantly non-wear time and very sedentary activity register as zero counts in accelerometer output. It has been observed that older adults, in particular those who are sedentary, can accumulate large periods of time without recording activity counts while wearing an accelerometer (Hutto et al. 2013). In addition periods of non-wear may occasionally

contain an epoch of spurious activity counts considered not to be wear time but rather movement of the monitor when not worn (Evenson and Terry 2009). The above factors have important ramifications for sedentary populations such as CKD 5, where periods of prolonged inactivity such as HD therapy sessions and television watching may be erroneously classified as non-wear time and not sedentary time.

Shorter periods of zero counts (ie: 20 consecutive zeroes) denoting non-wear are more appropriate for children (Masse et al. 2005). A threshold of 100 consecutive zero counts with allowance for two minutes of <100 counts has been recommended for monitoring adults (Troiano et al. 2008). Thresholds of 90 to 180 minutes of consecutive zero counts provide a stable assessment of wear hours and enable optimal data retention in middle aged and older adults with and without knee osteoarthritis (Song et al. 2010; Hutto et al. 2013). Moreover, 60 and 180 consecutive zero counts with allowance for a minute of spurious activity data (<100 cpm) are similarly accurate in classifying non-wear and sedentary time in sedentary office staff (Oliver et al. 2011). Haemodialysis therapy sessions vary in length from three to five hours, with people often remaining motionless or sleeping during that time. Consequently, non-wear time was determined by a threshold of 150 consecutive zero count minutes with allowance for less than one minute of spurious data of <100 cpm.

Participant data were inspected after application of the wear time filter to ensure all dialysis sessions were appropriately classified as sedentary time and not non-wear periods. Accumulating more than 18 hours monitor wear per day has been deemed to be outside regular waking hours and a criterion for data exclusion (Alhassan et al. 2008). In the event that the monitor was worn for more than this threshold a logical ‘waking hour’ day was triangulated using a combination of the following: monitor wear log; reported bedtimes from the Stanford seven-day recall questionnaire; and the first lie-to-stand and last stand-to-lie transitions from simultaneously recorded Activpal accelerometer data. Data outside the determined waking wear hours derived from bed mobility or nocturnal mobility was excluded from analysis.

Figure 2.15 Graphic presentation of participant GT3X data for one day.



2.5.5 Categorisation of Actigraph GT3X activity counts

Actigraph activity count output (figure 2.15) can be converted into categories reflecting the intensity of PA measured. Time spent in PA of differing levels of intensity (figure 2.16) was derived using the encumbent Actilife software cutpoints for light, lifestyle, moderate, vigorous and very vigorous PA developed by Freedson et al (1998). Time spent sedentary was determined via an activity count of less than 100 cpm (Matthews et al. 2008). Minute values for the different categories of PA intensity were normalised as a percentage of wear time so that PA outcomes could be compared across participants and with other populations (Hinkley et al. 2012). Actigraph activity counts and estimated step counts were reported as counts per day and similarly normalised to counts per minute of wear.

Figure 2.16 Participant GT3X data output following Actilife categorisation into PA intensity.

Monitor given to participant

Date	Sedentary	Light	Lifestyle	Moderate	Vigorous	Very Vigorous	Non-Wear	%Sedentary	%Light	%Lifestyle	%Moderate	%Vigorous	%Very Vigorous
14/02/12	7H 1M 0S	52M 15S	9M 15S	2M 45S	0S	0S	1H 54M 45S	86.76	10.77	1.91	0.57	0	0
15/02/12	10H 26M 45S	1H 29M 30S	25M 30S	5M 15S	0S	0S	11H 33M 0S	83.9	11.98	3.41	0.7	0	0
16/02/12	9H 33M 30S	1H 11M 45S	22M 15S	45M 15S	15S	0S	12H 7M 0S	80.43	10.06	3.12	6.35	0.04	0
17/02/12	11H 34M 45S	1H 29M 45S	17M 15S	13M 45S	0S	0S	10H 24M 30S	85.19	11.01	2.12	1.69	0	0
18/02/12	10H 31M 0S	1H 44M 30S	26M 30S	53M 45S	0S	0S	10H 24M 15S	77.35	12.81	3.25	6.59	0	0
19/02/12	9H 52M 0S	1H 19M 15S	16M 30S	6M 0S	0S	0S	12H 26M 15S	85.33	11.42	2.38	0.86	0	0
20/02/12	10H 14M 15S	1H 33M 0S	23M 15S	31M 15S	0S	0S	11H 18M 15S	80.64	12.21	3.05	4.1	0	0
21/02/12	11H 6M 45S	1H 21M 0S	46M 45S	42M 45S	0S	0S	10H 2M 45S	79.64	9.67	5.58	5.11	0	0
22/02/12	4H 26M 0S	49M 30S	18M 45S	27M 45S	0S	0S	7H 58M 0S	73.48	13.67	5.18	7.67	0	0

Monitor collected from participant

2.5.6 ActivPAL™ activity monitor

The ActivPAL™ accelerometer (PAL Technologies Ltd, Glasgow) is an activity monitor, which objectively estimates time spent in various PA behaviours (ie: sitting, standing, walking, sit to stand transitions, and steps) as opposed to intensity of PA. The monitor contains a uniaxial piezoresistive accelerometer which registers posture output and steps taken from thigh inclination. Time spent in different postures, transitions and steps performed are derived via algorithms embedded in the ActivPAL™ system software. The ActivPAL™ can collect data at a frequency of 10Hz and has enough battery life and memory capacity to record PA data for more than eight days. The ActivPAL™ monitors were recharged and initialised via a PAL Technologies Ltd docking station using the manufacturer's proprietary software installed on a laptop PC. The ActivPAL™ was initialised to capture data over 15 second epochs to synchronise with the Actigraph and was set up to start data collection following the participant's physical assessment.

2.5.7 ActivPAL wear protocol

Participants were given uniform scripted instructions on wear time and positioning of the ActivPAL™ both verbally and in a leaflet (appendix V a). Small and unobtrusive (about the size of a book of matches), the monitor was worn as per the instructions of PAL Technologies: on the front mid-line of the thigh a third of the way between the hip and knee of the non-dominant leg (figure 2.17). The monitor was held in place by a PAL*stickie* ™ and a short length of hypoallergenic tape or 3M Tegaderm™ transparent dressing.

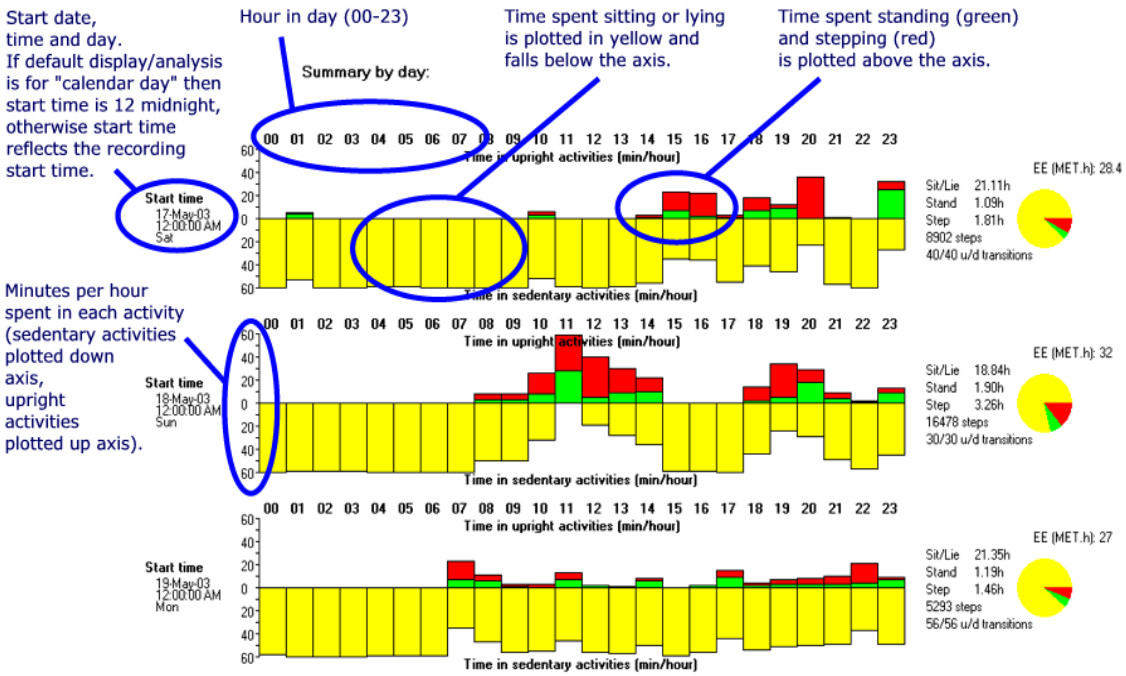
Figure 2.17 ActivPAL™ monitor and wear position.

The ActivPAL™ was worn during waking hours for eight days following the participant's physical assessment. The monitor was to be removed for bathing, showering, swimming and replaced again straight afterwards. Participants were also asked to note times when the monitor was put on and taken off using the wear log on the back of the monitor wear instructions (Appendix V b). The ActivPAL™ was collected from the participant on the eighth day after their physical assessment during a routine hospital visit for HD. Data were downloaded onto a laptop PC using the proprietary ActivPAL™ process and presentation software (Version 6.4.1).

2.5.8 ActivPAL™ data cleaning and classification of physical activity behaviours

As with the Actigraph data, the first day of ActivPAL wear was excluded from analysis as a practice day and the following seven days were used for analysis. Participants' ActivPAL™ data collected during free-living activity was processed using the ActivPAL™ Intelligent Activity Classification™ software which uses proprietary algorithms to classify raw monitor data into periods spent sitting, standing, and walking. Figure 2.18 illustrates how the ActivPAL™ software generates graphic representations of activity behaviours for each day of the week.

Figure 2.18 ActivPAL™ software presentation (V6.4.1) of physical activity behaviour (ACTIVPAL³ ™ OPERATING GUIDE, p. 9).



Step counts, transitions and energy expenditure (MET.h) can also be derived from participants' ActivPAL^{TM} data. The graphic output enabled files to be scrutinised for monitor malfunctions, identifying if the device had been worn upside down, and implausible data such as extended periods without steps being registered. The ActivPAL^{TM} operating guide states that a minimum duration of 10 seconds is required to register sitting and standing events. The ActivPAL^{TM} software calculates cadence as an average over 10 strides, and participants had to achieve a cadence of 20 steps per minute or greater before a walking event would be registered. A cadence below this threshold was not classified as walking.

Raw ActivPAL^{TM} data was exported to an Excel spreadsheet presenting the PA data in 15 second epochs. Participant data were then processed through a macro that determined sitting, standing and walking time in minutes. Time spent in these behaviours for a particular day was then converted into a percentage of monitor wear time determined as the period between the first sit-to-stand transfer and the last stand-to-sit transfer for that day. In addition PA counts and steps per day were subsequently reported per minute of monitor wear time.

2.5.9 Stanford 7-Day Recall questionnaire

The Stanford 7-day recall (7DR) questionnaire (Sallis et al. 1985) was used as a subjective/self-report method of estimating participant PA. The 7DR was chosen on the basis of favourable comparative psychometric properties and fitness for purpose (Terwee et al. 2010) in the HD population. The 7DR questionnaire (appendix VI) was administered via a one-to-one semi-structured interview format during a scheduled dialysis appointment. The interviewer preparation guidelines and the standardised script that accompanies the 7DR format (Sallis et al. 1985) were followed during questionnaire administration.

The 7DR was used to estimate participants' recollection of time spent in PA, strength and flexibility activities over the previous seven days. Time spent sleeping as well as frequency, duration, and intensity of PA (both leisure and work related) were recorded. Sleep time was defined as the period from when participants went to bed until they again got up to commence their daily activities (Sallis et al. 1985). Participants were made aware of how moderate to very hard intensity physical activity was differentiated from light intensity PA in order to exclude the latter (Sallis et al. 1985).

Time spent in discrete PA intensity levels (moderate, hard or very hard) per day was reported in minutes as long as the bouts were of 10 minutes duration or greater (Sallis et al. 1985). Type of PA engaged in was also recorded so that an energy expenditure value could be estimated as an outcome (table 2.2). Physiological cost in METs for each activity reported was obtained from the Compendium of Physical Activities (Ainsworth et al. 2011) and multiplied by the number of minutes for the activity to derive an energy expenditure value in MET minutes.

Table 2.2 Calculation of physical activity energy expenditure from 7DR.

Tuesday	Activity	MET cost	Calculation
Morning	20 minutes hoovering	3.5	20 x 3.5 = 70 MET mins
Afternoon	Attended dialysis therapy		
Evening	25 minute walk with dog	3.0	25 x 3.0 = 75 MET mins
Tuesday total PA related energy expenditure			145 MET minutes

2.6 Biochemistry

Biochemical results from the closest routine monthly bloods to each assessment (within the nearest two week period) were recorded for each participant. Bloods were taken in accordance with Scottish Renal Registry/Renal Association protocols and analysed in Monkland hospital's laboratory. Markers of clinical health monitored for during this project were: dialysis adequacy (urea reduction ration), haemoglobin, haematocrit, C-reactive protein, albumin, serum phosphate, corrected serum calcium, parathyroid, pre-dialysis creatinine. Blood results were obtained from the renal unit electronic patient record system (SERPR).

2.7 Medications

The number of prescribed medications at the time of each assessment was recorded for analysis of study outcomes. In addition, type and dose of vasoactive medications were also noted for subsequent discussion of results. Weekly prescribed dose of erthyropoiesis stimulating agents (ESA) such as darbepoetin alfa or aranesp as well as iron supplementation was recorded. Participant medication information was drawn from the renal unit's electronic patient record system (SERPR).

2.8 Comorbidity score

A simple additive comorbidity score was used to reflect the presence or absence of co-existing conditions at the time of assessment. Information regarding whether participants had a history of hypertension, diabetes, heart disease was drawn from the electronic patient records system (SERPR). Scores were not adjusted for severity of disease. Participants would therefore receive a comorbidity score of zero to three.

2.9 Anthropometric measurements

Participant weight was measured with a calibrated Salter 9018S electronic scale (Salter Housewares, Kent). Participants were instructed to dress in light clothing (shorts and shirt) and remove shoes before standing in the centre of the scale platform. Body mass was recorded to the nearest tenth of a kilogram (Eston and Reilly 2009). Height of participants was measured with a Leicester Height Measure stadiometer (Invicta Plastics Ltd, Leicester) in an upright standing position. Participants were instructed to stand with their back, buttocks and heels of both feet touching the stadiometer. The head was oriented in the Frankfurt plane with the lower border of the eye socket and the upper border of the ear opening aligned horizontally. Participants were then instructed to 'stretch upward' through their neck and head, take a full breath and briefly hold. The measurement rule was then lowered until it rested on the vertex of the head firmly, but without extreme pressure and height measurement taken to the nearest 0.05cm (Eston and Reilly 2009). Body mass index (BMI) was subsequently calculated using the following equation:

BMI = mass (kg) / height (m)^2.

Chapter 3: Minimum wear time recommendations for accelerometers

3.1 Introduction

Findings from epidemiological studies indicate level of self-reported physical activity (PA) is implicated in life expectancies of people receiving maintenance haemodialysis (HD) therapy for stage 5 CKD (O'Hare et al. 2003; Stack et al. 2005; Tentori et al. 2010). However, while PA questionnaires are expedient, cost-effective and nomothetically useful, they are susceptible to reporting error (Troiano et al. 2008; Townsend et al. 2010; Colley et al. 2011). Moreover, they have recognised limitations with quantifying activity at the lower end of the PA spectrum and time seated (Prince et al. 2008; Celis-Morales et al. 2012), which is a now a recognised risk factor for poor health outcomes (Owen et al. 2010; Thorp et al. 2011).

Consequently, there has been a shift towards increased use of objective assessment tools such as pedometers and accelerometers to estimate PA in stage 5 CKD. A range of activity monitor derived PA outcomes such as activity counts, steps taken, and energy expenditure are associated with health status and physical function in the HD population (Johansen et al. 2001a; Masuda et al. 2009; Kutsuna et al. 2010; Cupisti et al. 2011). One study even identified that a threshold of 50 minutes per day of all PA (>1.8 METs) estimated by accelerometer was independently predictive of improved survival among HD patients (Matsuzawa et al. 2012).

While general instrument validity has been established for many of these accelerometer assessment methods, there remains a need for standardisation of data reduction guidelines regarding accelerometer wear time. Minimum wear recommendations are necessary to ensure PA data are sufficiently reliable so that the ability to detect relationships with other variables is not diminished and conclusions drawn are not limited (Baranowski et al. 2008). Furthermore, reliable estimates of habitual PA are crucial for monitoring purposes to stratify risk, detect PA behaviour change, as well as to enable appropriate comparison and/or synthesis of findings across PA studies.

3.1.1 Accelerometer wear days and wear time

Participants in PA health studies are typically asked to wear accelerometers over seven consecutive days (Kristensen et al. 2010; Colley et al. 2011; Feinglass et al. 2011; Tudor-Locke et al. 2011d; Esliger et al. 2012), but despite reminders and

incentives, wear compliance is often variable (Baranowski et al. 2008; Rich et al. 2013). Moreover, monitor wear time during the day is usually discretionary and thus subject to variation both within and between participants (Hinkley et al. 2012). Investigators are therefore faced with important methodological considerations regarding how many hours of wear constitute a 'valid' day and how many days of accelerometer wear are required to provide reliable estimates of habitual PA and sedentary time (Masse et al. 2005; Troiano et al. 2008; Ojiambo et al. 2011).

Importantly, there is a trade off between applying criteria that are stringent enough to ensure data integrity while at the same time facilitating retention of an adequately representative sample size for subsequent analyses (Catellier et al. 2005; Hinkley et al. 2012). Even small differences in required wear time criteria can impact PA estimates as well as the number of participants retained, thereby potentially biasing sample representativeness (Masse et al. 2005; Chen et al. 2009; Tudor-Locke et al. 2011d; Toftager et al. 2013). Statistically based imputation methods may be employed to manage missing or incomplete data. However, performance of these algorithms is governed by the proportion of missing data, and difficulties with determining whether data are missing at random or not missing at random (Catellier et al. (2005). An alternative to deleting incomplete participant PA data is to establish the minimum required accelerometer wear time that reflects an individual's habitual activity with acceptable reliability. The first part of this process is to determine intra-individual PA variability between days (Baranowski and de Moor 2000). Intuitively, the greater the inter-day variability of estimated PA behaviours, the higher the number of wear-days and hours of accelerometer wear per day that will be required.

3.1.2 Accelerometer data reduction methods in CKD health research

Many of the previous studies using motion sensors to characterise PA of HD patients have lacked uniformity of methods. Number and type of days monitored (dialysis, non-dialysis, weekend) varies widely, often with no stated rationale. Studies employing arm-mounted devices have adopted 24-hour PA monitoring protocols (Baria et al. 2011; Mafra et al. 2011; Avesani et al. 2012), while the remainder required participants to wear hip mounted devices during waking hours. Notably, more than 80% of CKD studies did not define the number of wear hours required to 'rule in' a valid day, thus it would appear they have not explicitly at least, taken into account the effects of participants' discretionary wear on PA outcomes. Ten hours monitor wear is the most widely adopted standard to rule in a 'valid day'

(Trost et al. 2005; Tudor-Locke et al. 2011d), but there are indications less stringent wear thresholds may also provide sufficient outcome reliability in populations characterised by low PA (Chen et al. 2009). Accelerometer wear recommendations exist for sub-populations including: children (Ojiambo et al. 2011; Rich et al. 2013) asymptomatic adults (Matthews et al. 2002; Cook and Lambert 2008; Hart et al. 2011c) and low-active, overweight individuals (Chen et al. 2009). However, there are currently no minimum wear guidelines for clinical populations like stage 5 CKD.

Accelerometer data reduction in stage 5 CKD is beset with an additional challenge associated with treatment mode mediated variability of habitual PA. Patients are less active on dialysis days due to enforced inactivity during HD (Majchrzak et al. 2005), which effectively 'clamps' inter-patient PA variability for three days per week. Therefore it is possible wear time requirements may differ between dialysis and non-dialysis days. The influence of weekend PA variability may be a consideration when deciding whether to exclude participants. Debate remains with some studies arguing inclusion of at least one weekend day is necessary (Gretebeck and Montoye 1992; Ojiambo et al. 2011), while others contend there is no additional benefit to outcome reliability (McClain et al. 2010; Reid et al. 2013). This issue is perhaps more complex for HD patients, as some individuals are required to attend for treatment on a day which may represent a 'typical' weekend day for some and not for others.

3.1.3 Summary

Published guidance for PA surveillance via accelerometry is available for asymptomatic adults and children. However, no consensus recommendations presently exist for accelerometer data reduction methods in stage 5 CKD, and there appears to be low awareness of their importance. In light of strong evidence linking PA with health outcomes in stage 5 CKD and increased use of accelerometers, there is a need to establish data processing guidelines to underpin reliable estimation of habitual PA and sedentary behaviours.

The objectives of this study were to:

- Define the minimum number of days of accelerometry monitoring necessary to provide reliable estimates of habitual PA and sedentary behaviours of people undergoing maintenance HD.
- Determine a threshold for the minimum recommended accelerometer wear time hours required to define a valid data day for stage 5 CKD HD patients.
- Report the impact of different wear criteria on sample size retention.

3.2 Methods

3.2.1 Study design and participant recruitment

This was a reliability study involving 72 self-selected volunteer participants undergoing maintenance HD therapy for stage 5 CKD. Participants were recruited from an NHS outpatient HD unit at Monklands Hospital, Airdrie. Written informed consent was obtained. Approval for this study was obtained from the West of Scotland Research Ethics Service, Glasgow and Monklands Hospital Research and Development department, Airdrie (appendices I a and I b).

3.2.2 Objective measurement of physical activity outcomes

Physical activity data was collected for this study between November 2011 and August 2013. Physical activity was measured objectively via an Actigraph GT3X triaxial accelerometer (Actigraph Corp, Pensacola, Florida) and an ActivPAL accelerometer (PAL Technologies Ltd, Glasgow). ActivPAL and Actigraph accelerometers were synchronised and initialised using the proprietary software for each accelerometer installed on the same laptop (general methods 2.5.1 and 2.5.6). Participants wore both monitors as per general methods sections 2.5.2 and 2.5.7 during waking hours over a period of eight days, and a monitor wear log (appendices V a and V b) recorded when the monitors were put on and removed. Accelerometers were retrieved from participants on day nine, which coincided with a routine HD appointment and data downloaded .

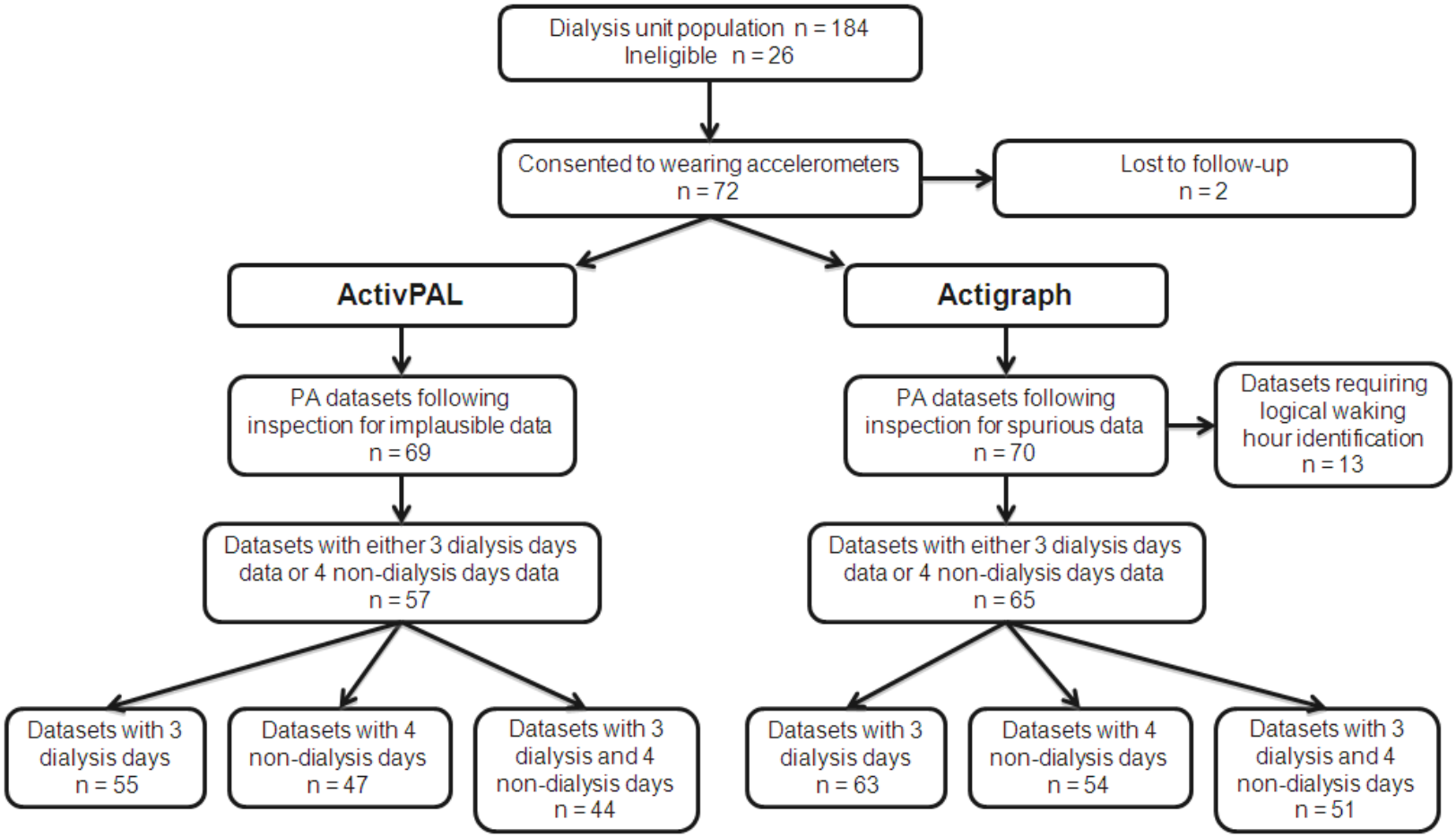
3.2.3 Data cleaning Actigraph GT3X

Wear time was to reflect a week of habitual PA, which included three dialysis days, and four non-dialysis days (comprising two midweek and two consecutive interdialytic days). Actigraph files were scrutinised for spurious data (general methods 2.5.3) and monitor wear time (general methods 2.5.4). Figure 3.3 describes the data cleaning and participant data inclusion process.

3.2.4 Data cleaning ActivPAL

ActivPAL data files were scrutinised implausible data and instances of monitor malfunction, and then exported to a Microsoft Excel spreadsheet to enable accurate determination of monitor wear times (general methods 2.5.8). The wear times were then entered into a Microsoft Excel macro, and time spent in different PA behaviours as a percentage of wear time for each day as well as, postural transitions, step counts and energy expenditure were derived.

Figure 3.1 Flowchart of PA data cleaning and inclusion for reliability analysis.



3.2.5 Categorisation of physical activity

Actigraph estimated sedentary time was defined as an activity count <100 cpm (Evenson et al. 2008; Matthews et al. 2008) while activity counts above this cutpoint were categorised as activity and thus contributed to estimated total PA time. Time spent in activity associated with a health enhancing effect was categorised as moderate to vigorous PA (MVPA) as superior inter-instrument reliability has been observed for this variable (McClain et al. 2007). The Freedson et al. (1998) cutpoint of ≥1952 cpm was used to determine MVPA.

ActivPAL estimated time in sitting/lying was used for the equivalent determination of time spent sedentary in line with the definition of sedentary behaviour as "a group of behaviours that occur whilst sitting or lying down and that require very low energy expenditure" (Pate et al. 2008). ActivPAL measured time in total PA was therefore derived from time spent in standing activities (walking, washing dishes, etc) in recognition of the fact that energy expenditure of postural skeletal muscle is greater than the <1.5 MET threshold defining sedentary behaviour (Pate et al. 2008). Energy expenditure (EE) outcomes calculated by the proprietary ActivPAL and Actigraph software and steps taken during the monitoring period for both devices was also reported. ActivPAL recorded (sit-to-stand) transitions were also reported.

3.2.6 Data Analysis

Actigraph derived PA outcome variables are reported as daily averages and include: sedentary time; total PA; moderate to vigorous PA (MVPA); steps; triaxial activity counts. Reported ActivPAL PA behaviours include: sit/lie time, stand time, stepping time, step counts, sit-to-stand transfers, and energy expenditure. All PA indices were normalised to total wear time to adjust for intra and inter-individual variation in wear time (Hinkley et al. 2012) as per general methods section 2.5.5. Transitions recorded by ActivPAL were normalised to hours of wear time.

The variance due to the hour or day effect was nested within subjects. Reported data were tested for normality using a Kolmogorov Smirnov test and presented as mean and standard deviation (SD) for continuous variables or median and interquartile range (IQR) for non-normally distributed data. To establish any treatment/non-treatment day effects accelerometer outcome data were tested for differences between dialysis days and non-dialysis days. Average values for each of the PA indices for dialysis days (three day average) and non-dialysis days (four day

average) were calculated and analyses performed for each hourly increment of wear time threshold from >4 hours to >10 hours wear per day (appendices VII and VIII).

Based on whether the data fulfilled the assumptions for parametric analysis differences in PA outcomes variables between different conditions (ie: dialysis versus non-dialysis days) were analysed using either a paired t-test or the Wilcoxon signed rank test (non-parametric equivalent). Level of significance was set at $p < 0.05$. Effect sizes were calculated to indicate the importance of any observed difference via *Cohen's d* (Equation 3.1) or *Pearson's r* (Equation 3.2) for parametric and non-parametric tests respectively.

Equation 3.1 *Cohen's d* parametric effect size calculation

$$d = \frac{\text{t value}}{\sqrt{\text{Sample size}}} \quad \text{(Cohen 1988)}$$

Equation 3.2 *Pearson's r* non-parametric effect size calculation

$$r = \frac{\text{Z Score}}{\sqrt{\text{Sample size}}} \quad \text{(Field 2012)}$$

Table 3.1 Below shows the thresholds for small, medium and large effect sizes for *Pearson's r* and *Cohen's d* (Cohen 1988; Cohen 1992).

Effect Size	Small	Medium	Large
Variance explained	1 %	9 %	25 %
Pearson's r	0.1	0.3	0.5
Cohen's d	0.2	0.5	0.8

Inter-day differences across the same condition (ie: dialysis days only) were examined using either a repeated measures analysis of variance (ANOVA) for normally distributed data with the calculated *F* value indicating the ratio of the systematic variance to the unsystematic variance (Field 2012). A Friedmans ANOVA (non-parametric equivalent) was employed for non-normally distributed data.

3.2.7 Calculation of accelerometer outcome variable reliability

To address the principal aim of this study, intra-class correlation coefficients (ICC) were computed to assess the variability of each accelerometer derived behaviour index across days of the week, based on increasing periods of wear time from four hours to >10 hours per day. The ICC calculation is a parametric test requiring data to be normally distributed. Physical activity variables defined as non-normally

distributed were therefore transformed according to the direction of their skew using either log transformation (positive skew) or square transformation (negative skew). The average measure and single measure reliability (ICC_{SM}) values were calculated for each PA variable on dialysis and non-dialysis days for every incremental wear threshold increase of one hour from four to ten hours. A two way random effects model ($ICC_{2,1}$) was employed where days were the random effect as the intention was to generalise calculated ICCs to other days of a similar condition within the same sample (Equation 3.3). In this equation σ_b is the 'between participant' variance and σ_w represents the 'within participant' variance. An ICC value approaching 1.0 indicates that the variability of observed outcomes is between- rather than within-participants. Average measure reliability values are reported to demonstrate stability of a given PA variable over three or four days (condition dependent) while the single measure ICC was employed in subsequent recommended wear time computations.

Equation 3.3 Intraclass correlation coefficient

$$ICC_{SM} = \sigma_b^2 / (\sigma_b^2 + \sigma_w^2)$$

(Shrout and Fleiss 1979)

3.2.8 Calculation of required accelerometer wear time

Minimum wear time recommendations were subsequently calculated by applying the Spearman Brown Prophecy formula (Equation 3.4) to the ICC_{SM}. The influence of incrementally increasing monitor wear time, and application of different levels of reliability were examined to demonstrate the implications of applying different criteria on computed wear time recommendations. The following levels of reliability were employed to determine wear recommendations: 0.70; 0.80; 0.90. In equation 3.4 'N' equals the recommended number of wear days and ICC_D is the desired reliability level and ICC_{SM} is the single measure of reliability.

Equation 3.4 Spearman-Brown prophecy formula

$$N=[ICC_D (1-ICC_D)] [(1-ICC_{SM}) ICC_{SM}]$$

(Stanley and Angoff 1971; Trost et al. 2005)

If the number of computed days was above a whole round number, the required wear time was rounded up to the next whole number as a conservative measure to ensure a minimum reliability criterion was maintained. The number of participants achieving the defined wear threshold was also calculated.

3.2.9 Calculation of a 'standard' wear day

Activity monitor wear times may vary between populations, therefore a 'standard' wear day was calculated according to the 80/70 method, whereby a standard day is defined as 80% of the time that 70% of participants wore their monitors. (Catellier et al. 2005; Masse et al. 2005). As habitual PA of people with stage 5 CKD is influenced by the unavoidable imposition of HD therapy sessions, a standard day was calculated for both dialysis and non-dialysis days.

3.3 Results

Participant characteristics are shown in table 3.2. Age of participants ranged from 24 to 87 years. Female participants made up a third of the overall sample while diabetes was present in nearly a quarter. Biomarkers of health and dialysis adequacy were within target ranges recommended by the UK renal Association guideline 2010. Minute by minute scrutiny of each of the 70 Actigraph accelerometer data files revealed no instances of physiologically implausible data. Thirteen participants were identified as having one or more days containing >18 hours of wear, for which logical waking-hour wear times were determined.

Table 3.2 Demographic and clinical characteristics of the sample.

	Total sample	Males	Females
n =	70	46	24
Diabetes	16 (23%)	11 (24%)	5 (21%)
Age (years)	55.9 ± 15.7 55.00 (44.0 - 70.5) §	58.8 ± 16.2 60.00 (49.8 - 73.0) §	50.2 ± 13.3 † 47.50 (42.3 - 54.3)
BMI (kg/m^2)	28.6 ± 6.4 † 27.7 (24.3 - 31.7)	28.0 ± 4.7 28.0 (24.5 - 30.6) §	29.7 ± 8.8 26.5 (23.6 - 34.9) §
Albumin (g/L)	38.6 ± 4.1 † 39.0 (36.0 - 42.0)	38.8 ± 4.4 † 39.5 (36.0 - 42.0)	38.3 ± 3.7 39.0 (36.0 - 41.0) §
Hb (g/dL)	11.3 ± 1.0	11.4 ± 1.0	11.0 ± 0.9
Dialysis adequacy (URR %)	71 (66 - 75)	69.00 (65.8 - 73.0)	75.0 (70.1 - 79.0)
Dialysis vintage (months)	15.8 (6.8 - 32.0)	17.2 (8.2 - 31.1)	9.4 (5.4 - 34.2)

§ Data normally distributed, median and interquartile range reported for comparison

†Data not normally distributed, mean and standard deviation reported for comparison

3.3.1 Accelerometer wear compliance

Overall compliance with Actigraph accelerometer wear was good with 51 (73%) participants wearing their monitor for seven consecutive days and a minimum of four hours on each day. Better compliance was observed on dialysis days with 63 (90%) wearing the monitors for all three dialysis days compared to 54 (77%) participants for all four non-dialysis days. No instances of monitor malfunction were observed. Fewer participants (n = 44, 63%) returned seven consecutive days of accelerometry data for the Activpal due to a combination of lower wear compliance and monitor malfunctions. As with the Actigraph monitor, wear compliance for the Activpal was better on dialysis days (n = 55, 79%) compared to non-dialysis days (n = 47, 67%).

3.3.2 Actigraph outcome variables

Normality of the seven-day averaged Actigraph outcome variables was assessed via Kolmogorov-Smirnov test as the sample size was >50. Only monitor wear time and minutes of time spent sedentary were normally distributed (appendix VII). The remaining accelerometer output indices (total PA, MVPA, activity counts, steps) were non-normally distributed (appendix VII). Accelerometer wear time and sedentary minutes were normally distributed variables for both the dialysis and non-dialysis day conditions. Sedentary time percentage and total PA (minutes and percentage of wear) were normally distributed for the non-dialysis day condition (appendix VII). All remaining Actigraph output variables were non-normally distributed. Table 3.3 presents the descriptive data for the Actigraph variables.

3.3.3 ActivPAL outcome variables

Normality of the seven-day averaged ActivPAL outcomes was assessed via Shapiro-Wilk test as the sample size <50. Monitor wear time, sit/lie and standing (mins/day), transfers and daily EE were normally distributed (appendix VIII). The remaining ActivPAL outcomes (stepping time and steps/day) and all indices normalised to wear time were non-normally distributed. Normality of PA variables for the dialysis and non-dialysis conditions was assessed via Kolmogorov-Smirnov and Shapiro-Wilk tests respectively (appendix VIII). Daily wear and EE were normally distributed. Minutes and percentage of sit/lie time, stand time percentage and transitions/hr for the dialysis day condition were normally distributed as was non-dialysis standing (mins). The remaining PA variables were non-normally distributed. ActivPAL accelerometer output data are presented descriptively in table 3.4.

Table 3.3 Actigraph accelerometer-derived estimates of PA and sedentary behaviour for stage 5 CKD HD patients. [normally distributed data are presented as Mean ± SD, and non-normally distributed data as Median (IQR)].

Condition	7 Days (n = 51)	Dialysis (n = 63)	Non-dialysis (n = 54)	Dialysis vs Non-dialysis	Effect size
Wear time (min)	798.8 ± 103.1	863.7 ± 124.9	750.2 ± 111.8	$t_{(50)} = 11.40$ $p < 0.001$	d = 1.60
Sedentary (min)	669.3 ± 114.5 670.5 (573.5 - 745.0)[§]	744.7 ± 114.8 749.3 (662.4, 819.2)[§]	612.8 ± 134.5 602.3 (528.3, 714.9)[§]	$t_{(50)} = 8.69$ $p < 0.001$	d = 1.22
Sedentary (%)	83.4 ± 8.9[†] 85.0 (78.9 - 90.2)	86.4 ± 6.6[†] 87.2 (83.2, 91.0)	81.2 ± 11.0 83.9 (75.0, 89.0)[§]	Z = -5.04 p < 0.001	r = 0.71
Total PA (min)	129.5 ± 69.9[†] 119.3 (84.4,154.5)	119.0 ± 69.9[†] 103.3 (81.2, 142.6)	137.4 ± 75.5 125.1 (86.9, 183.1)[§]	Z = -2.93 p = 0.003	r = 0.41
Total PA (%)	16.6 ± 8.9[†] 15.0 (9.8, 21.1)	13.6 ± 6.6[†] 12.8 (9.0, 16.8)	18.8 ± 11.0 16.1 (11.0, 25.0)[§]	Z = -5.04 p < 0.001	r = 0.71
MVPA (mins)	7.4 (2.1, 18.7)	6.1 (2.2, 10.6)	7.5 (1.8, 19.2)	Z = -2.89 p = 0.004	r = 0.40
MVPA (%)	0.9 (0.3, 2.3)	0.7 (0.3, 1.4)	0.9 (0.2, 3.0)	Z = -3.21 p = 0.001	r = 0.45
Triaxial counts	238457 (137399, 345520)	205964 (131019, 274379)	252010 (148901, 378802)	Z = -3.77 p < 0.001	r = 0.53
Triaxial cpm	303 (176, 397)	233.3 (151.4, 327.1)	322.1 (202.8, 473.0)	Z = -5.54 p < 0.001	r = 0.78
Steps	2303 (1048, 3876)	1935 (959, 2666)	2370 (1115, 4391)	Z = -3.05 p = 0.002	r = 0.43
Steps/min	2.8 (1.5, 5.0)	2.2 (1.4, 3.6)	3.3 (1.5, 5.4)	Z = -4.04 p < 0.001	r = 0.57

[§] Data normally distributed, Median and interquartile range reported for comparison.

[†] Data not normally distributed, Mean and standard deviation reported for comparison.

Table 3.4 ActivPAL accelerometer-derived estimates of PA and sedentary behaviour for stage 5 CKD HD patients. [normally distributed data are presented as Mean ± SD, and non-normally distributed data as Median (IQR)].

Condition	7 Days (n = 44)	Dialysis (n = 55)	Non-dialysis (n = 47)	Dialysis vs Non-dialysis	Effect Size
Wear (min)	801.7 ± 107.6	856.51 ± 134.8	745.05 ± 124.0	$T_{(43)} = 5.565$ $p < 0.001$	d =1.20
Sit/Lie (min)	701.8 ± 120.05 812.4 (714.2, 876.4) §	698.3 ± 122.6 694.57 (607.5, 785.16)§	524.7 ± 149.9† 532.4 (469.9, 642.9)	Z = -5.532 p < 0.001	r = 0.83
Sit/Lie (%)	74.89 ± 12.069† 76.9 (69.1, 84.1)	81.7 ± 9.5 82.97 (76.7, 87.4) §	70.0 ± 15.9† 71.56 (62.2, 82.6)	Z = -5.053 p < 0.001	r = 0.76
Step Time (min)	44.5 (29.2, 63.0)	32.1 (22.8, 47.7)	51.2 (29.6, 73.7)	Z = -4.260 p < 0.001	r = 0.64
Step Time (%)	4.06 (3.0, 6.3)	3.91 (2.8, 5.6)	6.6 (4.1, 10.6)	Z = -5.053 p < 0.001	r = 0.76
Stand (min)	197.3 ± 95.6 175.3 (127.5, 247.4) §	158.3 ± 94.5 † 141.0 (101.1, 197.2)	220.5 ± 113.1 213.0 (128.1, 283.5) §	Z = -3.980 p < 0.001	r = 0.60
Stand (%)	25.1 ± 12.1† 23.06 (16.0, 30.9)	18.3 ± 9.5 17.03 (12.6, 23.27) §	30.0 ± 15.9 † 28.4 (17.4, 37.8)	Z = -4.878 p < 0.001	r = 0.74
Transitions (day)	31.0 ± 10.1 29.3 (22.8, 37.8) §	30.5 ± 10.7† 28.3 (23.3, 37.3)	34.5 ± 10.6 33.25 (27.0, 41.3) §	$T_{(43)}$= -2.842 p = 0.007	d = 0.61
Transitions (hr)	2.6 ± 0.8† 2.5 (2.1, 2.9)	2.1 ± 0.7 2.05 (1.7, 2.5) §	2.9 ± 1.0† 2.80 (2.3, 3.2)	Z = -5.123 p < 0.001	r = 0.77
Steps/day	3242 (1909, 4615)	2189 (1493, 3577)	3594 (2055, 5854)	Z = -3.769 p < 0.001	r = 0.57
Steps/min	4.2 (2.5, 6.1)	2.76 (1.8, 3.7)	4.9 (2.6, 8.3)	Z = -4.621 p < 0.001	r = 0.70
METmin/day	1121.9 ± 172.2	1164.6 ± 215.6	1066.3 ± 180.5	Z = -3.349 p = 0.001	r = 0.50
METmin/min	1.37 (1.33, 1.42)	1.34 (1.31, 1.36)	1.40 (1.33, 1.49)	Z = -4.831 p < 0.001	r = 0.73

§ Data normally distributed, Median and interquartile range reported for comparison.

† Data not normally distributed, Mean and standard deviation reported for comparison.

3.3.4 Actigraph outcome variable analysis of day effect

Table 3.3 presents the results from statistical testing to determine the effect of different conditions (dialysis versus non-dialysis days) on accelerometer output variables. Mean accelerometer wear time across the seven days was 798.8 min ± 103.1 min (13.3 hours ± 1.7 hours), however average monitor wear time for dialysis days (863.7 min ± 124.9) was significantly longer ($p < 0.001$) compared to non-dialysis days (750.2 min ± 111.8) as indicated by paired t-test (large effect). Participants spent significantly more time sedentary on dialysis days (large effect) compared to non-dialysis days both in overall minutes (figure 3.2) and as a percentage of wear time ($p < 0.001$). Non-parametric comparison using the Wilcoxon signed rank test demonstrated less time was spent in total PA on dialysis days compared to non-dialysis days in minutes (medium effect, $p = 0.003$) and as a percentage of wear time (large effect, $p < 0.001$). In addition accelerometer counts per minute and steps per minute of wear time were also significantly greater (large effect, $p < 0.001$) on non-dialysis days compared to dialysis day. These findings remained consistent when incremental increases in monitor wear thresholds four to 10 hours were applied (appendix IX)

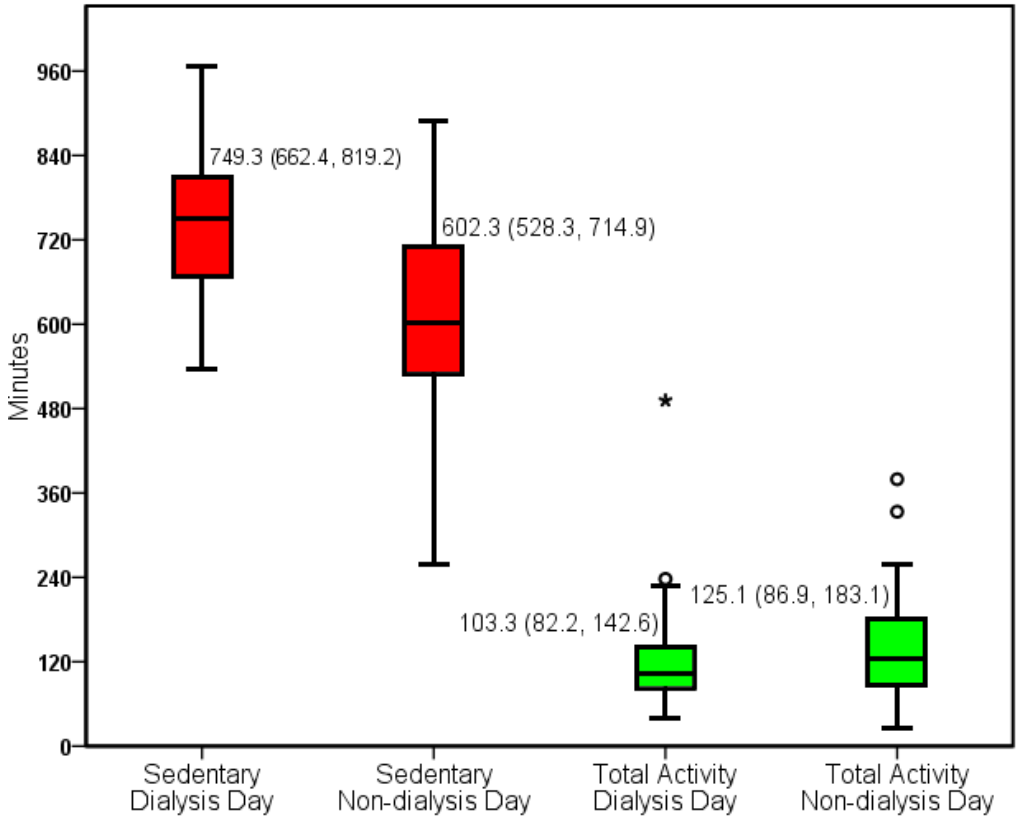
Table 3.5 Determination of Actigraph-derived PA outcome variable differences across the same condition (dialysis and non-dialysis days).

Condition	Dialysis Days only	Non-Dialysis Days only
Wear (min)	0.93, $F_{(2,124)} = 2.38$ $p = 0.10$	0.94, $F_{(3, 51)} = 1.01$ $p = 0.40$
Sedentary(min)	0.92, $F_{(2,124)} = 2.50$ $p = 0.09$	0.98, $F_{(3, 51)} = 0.38$ $p = 0.78$
Sedentary (%)	$X^{2(2)} = 0.13$ $p = 0.94$	0.95, $F_{(3, 51)} = 0.86$ $p = 0.47$
Total PA (min)	$X^{2(2)} = 0.87$ $p = 0.65$	0.90, $F_{(3, 51)} = 1.86$ $p = 0.15$
Total PA (%)	$X^{2(2)} = 0.13$ $p = 0.94$	0.95, $F_{(3, 51)} = 0.86$ $p = 0.47$
MVPA (min)	$X^{2(2)} = 2.76$ $p = 0.25$	$X^{2(2)} = 5.29$ $p = 0.15$
MVPA (%)	$X^{2(2)} = 0.98$ $p = 0.61$	$X^{2(2)} = 4.29$ $p = 0.23$
Triaxial counts/day	$X^{2(2)} = 4.03$ $p = 0.13$	$X^{2(3)} = 4.96$ $p = 0.18$
Triaxial cpm	$X^{2(2)} = 2.32$ $p = 0.31$	$X^{2(3)} = 3.27$ $p = 0.35$
Steps	$X^{2(2)} = 0.15$ $p = 0.93$	$X^{2(3)} = 5.59$ $p = 0.20$
Steps/min	$X^{2(2)} = 0.60$ $p = 0.74$	$X^{2(3)} = 1.31$ $p = 0.73$

Results of statistical testing for differences across the same condition (dialysis or non-dialysis days) are presented in table 3.5. Data from 63 participants were used to determine whether there was a significant day effect for Actigraph PA outcomes

across dialysis days only, while data from 54 participants was used for non-dialysis days. A one-way repeated measures ANOVA revealed that there was no significant day effect on accelerometer wear time (p = 0.10), and minutes spent sedentary across the three dialysis days (p = 0.09). The same result was observed for monitor wear (p = 0.40), sedentary time (minutes, p = 0.78 and percentage, p = 0.47) and total PA (minutes, p = 0.15 and percentage, p = 0.47) across the four non-dialysis days. Friedman's ANOVA indicated no significant day effect for percentage of sedentary time (p = 0.94), total PA (minutes, p 0.65 and percentage, p = 0.94), MVPA (minutes, p = 0.25 and percentage, p = 0.61) triaxial counts (per day, p = 0.13 and per minute, p = 0.31) or steps performed (per day, p = 0.93 and per minute, p = 0.74) for the dialysis day condition. Accordingly, the same non-parametric test showed no significant day effect for MVPA (minutes, p = 0.15 and percentage, p = 0.23), triaxial counts or steps (per day, p = 0.18 and per min, p = 0.35) performed for the non-dialysis day condition.

Figure 3.2 Graph of Actigraph estimated time (minutes) spent in sedentary and total PA for dialysis versus non-dialysis days (median and IQR).



3.3.5 ActivPAL outcome variable analysis of day effect

Results presented in table 3.4 show ActivPAL estimated PA outcomes were significantly different on dialysis days compared to non-dialysis days. Mean accelerometer wear time across the seven days was 801.7 ± 107.6 min (13.4 hours ± 1.8 hours). ActivPAL wear time was significantly longer ($p < 0.001$) on dialysis days (856.51 ± 134.8) compared to non-dialysis days (745.05 ± 124.0). In addition significantly fewer sit-to-stand transfers were performed on dialysis days as indicated by paired t-test (medium effect, $p = 0.007$). Non-parametric comparison using the Wilcoxon signed rank test was employed for the remaining ActivPAL PA indices. Significantly more time was spent seated or lying on dialysis days compared to non-dialysis (large effect, $p < 0.001$) while less time was spent in PA involving standing both in overall minutes (figure 3.3) and as a percentage of wear time (large effect, $p < 0.001$). Participants spent more time stepping, performed more steps, and had higher estimated energy expenditure on non-dialysis compared to dialysis days ($p < 0.001$) with large effect sizes uniformly observed.

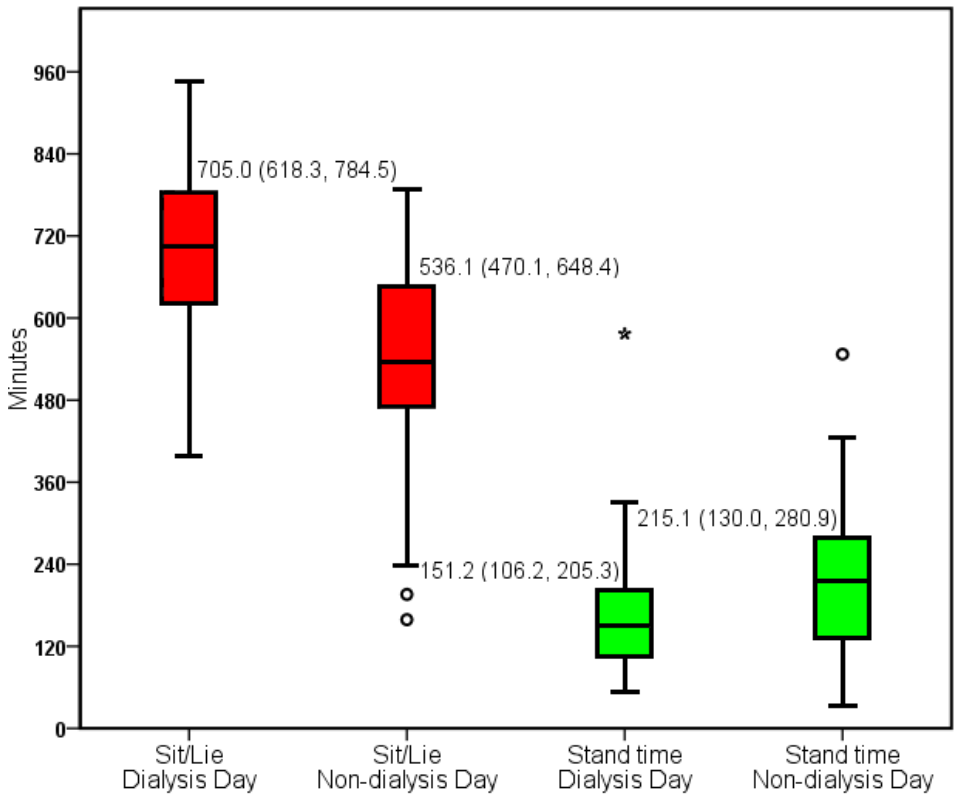
Table 3.6 Determination of ActivPAL-derived outcome variable differences across the same condition (dialysis and non-dialysis days).

Condition	Dialysis Days	Non-Dialysis Days
Wear (min)	$0.99, F_{(2,108)} = 0.21$ $p = 0.10$	$0.98, F_{(3,44)} = 0.36$ $p = 0.79$
Sit/Lie (min)	$0.99, F_{(2,108)} = 0.33$ $p = 0.72$	$X^{2(2)} = 2.21$ $p = 0.53$
Sit/Lie (%)	$0.98, F_{(2,108)} = 0.51$ $p = 0.09$	$X^{2(2)} = 6.65$ $p = 0.08$
Stand (mins)	$X^{2(2)} = 1.56$ $p = 0.46$	$F_{(2.1, 97.7)} = 0.83$ $p = 0.45$
Stand (%)	$0.98, F_{(2,108)} = 0.52$ $p = 0.60$	$X^{2(2)} = 6.65$ $p = 0.08$
Stepping (min)	$X^{2(2)} = 0.44$ $p = 0.80$	$X^{2(2)} = 3.33$ $p = 0.34$
Step Time (%)	$X^{2(2)} = 1.78$ $p = 0.41$	$X^{2(2)} = 1.90$ $p = 0.59$
Transitions/day	$X^{2(2)} = 0.15$ $p = 0.93$	$0.89, F_{(3,44)} = 1.96$ $p = 0.14$
Transitions/hr	$0.23, F_{(1.7,92)} = 0.35$ $p = 0.67$	$X^{2(3)} = 5.221$ $p = 0.16$
Steps/day	$X^{2(2)} = 0.436$ $p = 0.80$	$X^{2(3)} = 3.817$ $p = 0.28$
Steps/min	$X^{2(2)} = 1.782$ $p = 0.41$	$X^{2(3)} = 0.932$ $p = 0.82$
EE/day	$0.99, F_{(2,108)} = 0.15$ $p = 0.86$	$F_{(2.4, 108.6)} = 1.96$ $p = 0.14$
EE/min	$X^{2(2)} = 2.218$ $p = 0.33$	$X^{2(3)} = 2.719$ $p = 0.44$

Results of ANOVA analysis examining differences across the same condition (table 3.6) revealed that there was no significant day-effect on accelerometer wear time, time seated/lying, standing, transitions per hour, and energy expenditure per day

across the three dialysis days. Similarly, no significant differences were observed for monitor wear, standing time (minutes), transitions (per day) and daily EE across the four non-dialysis days. Non-parametric Friedman's ANOVA also showed no significant day effect for the remaining ActivPAL outcome variables across either the three days of the dialysis condition or the four days of the non-dialysis condition.

Figure 3.3 Graph of ActivPAL time spent sitting/lying and in standing activities for dialysis days versus non-dialysis days (median and IQR).



3.3.6 Actigraph outcome variable reliability analysis

Tables 3.5.1 and 3.5.2 show the average measure intraclass correlation coefficients for each accelerometer outcome variable for dialysis days and non-dialysis days respectively. Single and average measure ICCs were stable between >4 and >10 hours wear on dialysis days (appendix XI). A trend for higher reliability is observed with incremental increases in wear time for most of the PA variables with sedentary minutes showing the most noticeable improvement. Physical activity outcome variables on non-dialysis days are similarly stable. Reliability coefficients for some of the variables decline slightly as the sample size available for analysis drops below 50. Physical activity outcome variables with the highest reliability are triaxial activity

counts and step counts while the variable with lowest reliability is estimated minutes of sedentary time.

Table 3.7 Actigraph average measure ICC values for outcome variables over three dialysis days.

Hours of wear	>4	>5	>6	>7	>8	>9	>10
Cases (n=)	63	63	62	60	57	55	53
Sedentary mins	0.66	0.66	0.71	0.77	0.84	0.83	0.81
Sedentary %	0.91	0.91	0.91	0.92	0.92	0.92	0.93
Total PA mins	0.90	0.90	0.91	0.91	0.92	0.92	0.92
Total PA %	0.90	0.90	0.91	0.92	0.92	0.92	0.92
MVPA mins	0.92	0.92	0.93	0.92	0.92	0.92	0.92
MVPA %	0.91	0.91	0.91	0.91	0.91	0.91	0.91
Triaxial cpd	0.92	0.92	0.93	0.93	0.93	0.93	0.93
Triaxial cpm	0.93	0.93	0.93	0.94	0.94	0.94	0.94
Steps/day	0.95	0.95	0.95	0.95	0.95	0.95	0.95
Steps/min	0.95	0.95	0.95	0.95	0.95	0.95	0.95

Table 3.8 Actigraph average measure ICC values for outcome variables over four non-dialysis days.

Wear time	>4	>5	>6	>7	>8	>9	>10
Cases (n =)	54	52	52	51	40	38	32
Sedentary mins	0.83	0.81	0.81	0.82	0.85	0.85	0.84
Sedentary %	0.93	0.93	0.93	0.93	0.92	0.92	0.89
Total PA mins	0.92	0.93	0.93	0.93	0.92	0.92	0.90
Total PA %	0.94	0.94	0.94	0.94	0.94	0.94	0.92
MVPA mins	0.95	0.95	0.95	0.95	0.95	0.94	0.94
MVPA %	0.95	0.95	0.95	0.95	0.95	0.94	0.94
Triaxial cpd	0.94	0.94	0.94	0.94	0.93	0.93	0.93
Triaxial cpm	0.95	0.95	0.95	0.95	0.95	0.95	0.94
Steps	0.95	0.96	0.96	0.96	0.95	0.95	0.95
Steps/min	0.96	0.96	0.96	0.96	0.96	0.96	0.95

3.3.7 ActivPAL outcome variable reliability analysis

Average measure ICCs for ActivPAL outcome variables on dialysis days and non-dialysis days are presented in tables 3.9 and 3.10. Single measure (appendix XII) and average measure ICCs are relatively stable between >4 and >10 hours wear on both dialysis and non-dialysis days. Physical activity variables on non-dialysis days show a trend for declining reliability with higher thresholds of monitor wear, particularly from six hours as the number of datasets diminishes below 45 (table 3.9). Time spent seated/lying (minutes per day) shows consistently lower reliability

for both dialysis and non-dialysis days than other outcomes but when normalised to wear time this variable has the same reliability as percentage of time spent in standing activities.

Table 3.9 ActivPAL average measure ICC values for outcome variables over three dialysis days.

Hours of wear	>4	>5	>6	>7	>8	>9	>10
Cases (n =)	55	55	52	51	51	49	44
Sit/Lie mins	0.72	0.72	0.80	0.81	0.81	0.82	0.87
Sit/Lie %	0.94	0.94	0.94	0.94	0.94	0.94	0.94
Stand mins	0.87	0.87	0.87	0.88	0.88	0.85	0.87
Stand %	0.94	0.94	0.94	0.94	0.94	0.94	0.94
Stepping mins	0.90	0.90	0.92	0.92	0.92	0.91	0.91
Stepping %	0.91	0.91	0.91	0.91	0.91	0.91	0.91
Steps/day	0.90	0.90	0.92	0.92	0.92	0.91	0.91
Steps/min	0.91	0.91	0.91	0.91	0.91	0.91	0.91
Transitions/day	0.76	0.76	0.82	0.80	0.80	0.76	0.80
Transitions/hr	0.76	0.76	0.79	0.78	0.78	0.77	0.83
EE/day	0.78	0.78	0.87	0.88	0.88	0.87	0.92
EE/min	0.93	0.93	0.94	0.94	0.94	0.93	0.95

Table 3.10 ActivPAL average measure ICC values for outcome variables over four non-dialysis days.

Hours of wear	>4	>5	>6	>7	>8	>9	>10
Cases (n =)	47	45	43	43	37	34	24
Sit/Lie mins	0.84	0.82	0.84	0.84	0.80	0.81	0.77
Sit/Lie %	0.90	0.90	0.89	0.89	0.88	0.86	0.89
Stand mins	0.89	0.90	0.88	0.88	0.88	0.85	0.90
Stand %	0.91	0.90	0.88	0.88	0.87	0.85	0.88
Stepping mins	0.91	0.92	0.92	0.92	0.91	0.90	0.91
Stepping %	0.93	0.93	0.92	0.92	0.91	0.91	0.91
Steps/day	0.92	0.93	0.93	0.93	0.92	0.91	0.92
Steps/min	0.93	0.93	0.93	0.93	0.92	0.92	0.91
Transitions/day	0.82	0.83	0.83	0.83	0.82	0.76	0.73
Transitions/hr	0.88	0.89	0.89	0.89	0.89	0.87	0.84
EE/day	0.70	0.79	0.81	0.81	0.81	0.75	0.83
EE/min	0.93	0.94	0.94	0.94	0.92	0.92	0.91

3.3.8 Actigraph outcome variable wear time recommendations

Tables 3.11 to 3.14 show the computed wear times for accelerometer outcome variables according to wear time to define a valid day and application of desired level of reliability (0.70, 0.80, 0.90). The more stringent the desired reliability, the greater the number of days and hours of wear within those days hours required. In general the more hours the monitor is worn the fewer days are required. For this sample of HD patients just under one dialysis day with a minimum of seven hours wear is required to achieve a reliability level of 0.80 for sedentary behaviour on dialysis days (table 3.11). Similarly one dialysis wear day with a slightly lower threshold of six hours is required to reliably estimate total PA (table 3.12). For non-dialysis days more than one day but less than two days wear is required to achieve a reliability level of 0.80 for sedentary behaviour and total PA. In contrast to the wear threshold for dialysis days, inclusion of accelerometer datasets with as little as four hours of data does not appear to increase the number of days required for reliable estimates of sedentary behaviour and total PA (normalised to wear time) on non-dialysis days. Furthermore, a wear time threshold of seven hours may decrease the required number of non-dialysis days to reliably measure total PA to just one.

Wear time requirements vary depending on the PA outcome variable. Activity counts and steps per minute required just one dialysis day and one non-dialysis day with inclusion of datasets with as few as four hours wear (tables 3.13 and 3.14). Two dialysis and one non-dialysis days are required for reliable estimation of MVPA normalised to wear time (appendix XIV a). When time spent sedentary is not normalised to wear time, required number of wear days for a reliability of 0.80 increases substantially to three dialysis and three non-dialysis days with a minimum wear threshold of eight hours per day (appendix XIII a). Wear time required for total PA in minutes per day increases slightly to two dialysis days and two non-dialysis days (appendix XIII b). In contrast computed wear for MVPA in minutes per day is slightly less at one dialysis and one non-dialysis day allowing inclusion of datasets with as little as six hours/day (appendix XIII c). Wear time requirement for activity counts per day remains unchanged at one day of each condition as long as a minimum wear threshold of six hours is observed (appendix IV b). Likewise recommended wear for reliable measurement of steps/day remains unchanged at one dialysis and one non-dialysis day as long as a wear threshold of five hours is observed (appendix IV c).

Table 3.11 Computed Actigraph wear for sedentary time (percent).

Dialysis Day Sedentary %					Non-Dialysis Day Sedentary %				
n =	Wear hours	Days required for desired reliability 0.7	0.8	0.9	n =	Wear hours	Days required for desired reliability 0.7	0.8	0.9
63	4h	0.69	1.19	2.67	54	4h	0.74	1.26	2.84
63	5h	0.69	1.19	2.67	52	5h	0.70	1.21	2.72
62	6h	0.67	1.15	2.58	52	6h	0.70	1.21	2.72
60	7h	0.58	0.99	2.24	51	7h	0.68	1.16	2.62
57	8h	0.57	0.98	2.21	40	8h	0.79	1.35	3.05
55	9h	0.58	1.00	2.24	38	9h	0.80	1.38	3.10
53	10h	0.56	0.96	2.16	32	10h	1.15	1.97	4.43

Table 3.12 Computed Actigraph wear for total PA (percent).

Dialysis Day Total PA %					Non-Dialysis Day Total PA %				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
63	4h	0.59	1.01	2.26	54	4h	0.59	1.02	2.29
63	5h	0.59	1.01	2.26	52	5h	0.59	1.02	2.29
62	6h	0.55	0.94	2.11	52	6h	0.59	1.02	2.29
60	7h	0.53	0.91	2.05	51	7h	0.57	0.97	2.19
57	8h	0.52	0.89	2.00	40	8h	0.64	1.10	2.47
55	9h	0.51	0.88	1.98	38	9h	0.62	1.06	2.38
53	10h	0.52	0.89	2.00	32	10h	0.82	1.41	3.17

Table 3.13 Computed Actigraph wear for triaxial counts/minute.

Dialysis Day Triaxial cpm					Non-Dialysis Day Triaxial cpm				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
63	4h	0.53	0.91	2.04	54	4h	0.44	0.76	1.71
63	5h	0.53	0.91	2.04	52	5h	0.45	0.77	1.74
62	6h	0.52	0.89	2.01	52	6h	0.45	0.77	1.74
60	7h	0.47	0.81	1.82	51	7h	0.44	0.76	1.70
57	8h	0.47	0.80	1.80	40	8h	0.51	0.87	1.97
55	9h	0.46	0.80	1.79	38	9h	0.51	0.87	1.97
53	10h	0.45	0.77	1.73	32	10h	0.58	0.99	2.23

Table 3.14 Computed Actigraph wear for steps/minute.

Dialysis Day Steps/min					Non-Dialysis Day Steps/min				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
63	4h	0.38	0.65	1.47	54	4h	0.44	0.76	1.70
63	5h	0.38	0.65	1.47	52	5h	0.41	0.71	1.59
62	6h	0.38	0.64	1.45	52	6h	0.41	0.71	1.59
60	7h	0.36	0.61	1.38	51	7h	0.41	0.71	1.59
57	8h	0.35	0.60	1.35	40	8h	0.50	0.85	1.91
55	9h	0.35	0.60	1.35	38	9h	0.49	0.84	1.89
53	10h	0.35	0.59	1.33	32	10h	0.51	0.87	1.97

3.3.9 ActivPAL outcome variable wear time recommendations

Computed wear times for ActivPAL outcome variables according to desired level of reliability (0.70, 0.80, 0.90) are presented in tables 3.15 to 3.18. Spearman-Brown Prophecy calculations indicate just one dialysis day is required to obtain reliable ActivPAL estimates of time spent seated/lying and in standing activities as a percentage of monitor wear time (tables 3.15 and 3.16). Moreover, the number of wear days required remains unchanged when datasets with as low as five hours wear are included. Computations for the same outcomes on non-dialysis days indicate two days are required when accelerometry data with as few as four hours wear are included (tables 3.15 and 3.16). Wear time required starts to increase beyond two days above thresholds of seven hours and five hours (for sit/lie and stand time respectively) as the number of datasets available for analysis drops below a sample size of 45. Estimated steps per minute requires just over two dialysis and two non-dialysis wear days to achieve a reliability level of 0.80 (table 3.17), while similarly reliable estimates of energy expenditure can be obtained from just one day of each condition (table 3.18).

Recommended number of wear days are generally greater for ActivPAL outcome variables not adjusted for wear time. A full week of ActivPAL wear is required to achieve clinically acceptable reliable estimates of minutes per day spent seated/lying (appendix XV a). For reliable estimates of minutes per day spent in standing activities the computed requirement is slightly less at two dialysis days and three non-dialysis days (appendix XV b). Meanwhile, two days of each condition are recommended for stepping time (appendix XV c and XVI a) and steps taken per day (appendix XVI b). A full week is recommended to reliably estimate sit-to-stand transfers with a minimum of six hours monitor wear per day (appendix XVI c). Using the same minimum wear threshold of six hours, daily energy expenditure estimates can be derived reliably from two dialysis days and four non-dialysis days of ActivPAL data (Appendix XVII a and XVII b).

Table 3.15 Computed ActivPAL wear for sit/lie time (percent).

Dialysis Day					Non-Dialysis Day				
n =	Wear hours	Days required for desired reliability 0.7	0.8	0.9	n =	Wear hours	Days required for desired reliability 0.7	0.8	0.9
55	4h	0.47	0.80	1.80	47	4h	1.01	1.74	3.90
55	5h	0.47	0.80	1.80	45	5h	1.04	1.78	4.01
52	6h	0.47	0.80	1.80	43	6h	1.12	1.93	4.34
51	7h	0.46	0.79	1.77	43	7h	1.12	1.93	4.34
51	8h	0.46	0.79	1.77	37	8h	1.33	2.27	5.12
49	9h	0.48	0.83	1.86	34	9h	1.48	2.54	5.72
44	10h	0.42	0.72	1.62	24	10h	1.16	1.99	4.48

Table 3.16 Computed ActivPAL wear for stand time (percent).

Dialysis Day					Non-Dialysis Day				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
55	4h	0.47	0.80	1.80	47	4h	0.95	1.63	3.66
55	5h	0.47	0.80	1.80	45	5h	0.98	1.69	3.80
52	6h	0.47	0.80	1.80	43	6h	1.27	2.18	4.90
51	7h	0.46	0.79	1.77	43	7h	1.27	2.18	4.90
51	8h	0.46	0.79	1.77	37	8h	1.44	2.47	5.57
49	9h	0.48	0.83	1.86	34	9h	1.66	2.85	6.42
44	10h	0.42	0.72	1.62	24	10h	1.31	2.25	5.05

Table 3.17 Computed ActivPAL wear for steps/minute.

Dialysis Day					Non-Dialysis Day				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
55	4h	0.72	1.24	2.80	47	4h	0.67	1.14	2.57
55	5h	0.72	1.24	2.80	45	5h	0.67	1.14	2.57
52	6h	0.67	1.15	2.59	43	6h	0.70	1.19	2.68
51	7h	0.65	1.12	2.52	43	7h	0.70	1.19	2.68
51	8h	0.65	1.12	2.52	37	8h	0.79	1.35	3.05
49	9h	0.73	1.25	2.81	34	9h	0.83	1.41	3.18
44	10h	0.71	1.21	2.72	24	10h	0.87	1.50	3.37

Table 3.18 Computed ActivPAL wear energy expenditure/min.

Dialysis Day					Non-Dialysis Day				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
55	4h	0.54	0.93	2.09	47	4h	0.54	0.93	2.09
55	5h	0.54	0.93	2.09	45	5h	0.54	0.93	2.09
52	6h	0.49	0.83	1.88	43	6h	0.49	0.83	1.88
51	7h	0.48	0.82	1.84	43	7h	0.48	0.82	1.84
51	8h	0.48	0.82	1.84	37	8h	0.48	0.82	1.84
49	9h	0.50	0.85	1.92	34	9h	0.50	0.85	1.92
44	10h	0.41	0.70	1.57	24	10h	0.41	0.70	1.57

3.3.10 Actigraph and ActivPAL standard wear day calculation

The 70th percentile of the averaged Actigraph wear times dialysis days and non-dialysis days was 932 minutes and 827 minutes respectively. For the ActivPAL similar wear times of 947 minutes and 814 minutes (dialysis and non-dialysis days respectively) were observed. A standard wear day was then defined as 80 percent of these values. This translated to 757 minutes (12.6 hours) for Actigraph and 756 minutes (12.6 hours) for ActivPAL on dialysis days and 662 minutes (11.0 hours) and 651 minutes (10.9 hours) for Actigraph and ActivPAL respectively on non-dialysis days. This result is a more stringent criterion than the 10 hour/day standard commonly adopted for data reduction.

Table 3.19 illustrates participant compliance with accelerometer wear according to the number of days monitors were worn and for each wear threshold to define a valid day from a minimum of six hours to the widely applied standard of 10 hours. Clearly, the more stringent the wear time requirement the greater the percentage of the sample that would be excluded from final analyses. All participants returned Actigraph PA data containing at least one dialysis day with a minimum of 10 hours wear, and all but two (97.1 %) for the ActivPAL. Comparatively fewer participants returned Actigraph and ActivPAL monitors with at least two non-dialysis days and 10 hours wear (87.1% and 84.3% respectively). The number of individuals retained for final analyses is therefore governed by the number participants returning sufficient non-dialysis day wear. Application the '70/80 rule' standard wear-day criterion as calculated for this sample would have a similar or more pronounced effect on reducing participant retention.

Table 3.19 Number of participants (*n*, %) according to minimum daily wear time thresholds and wear days for Actigraph and Activpal accelerometer data.

Monitor wear criteria	>6 hours		>7 hours		>8 hours		>9 hours		>10 hours	
	Actigraph	Activpal	Actigraph	Activpal	Actigraph	Activpal	Actigraph	Activpal	Actigraph	Activpal
Dialysis days ≥1	70 (100)	69 (98.6)	70 (100)	69 (98.6)	70 (100)	69 (98.6)	70 (100)	68 (97.1)	70 (100)	68 (97.1)
Dialysis days ≥2	68 (97.1)	64 (91.4)	68 (97.1)	64 (91.4)	67 (95.7)	64 (91.4)	67 (95.7)	63 (90)	65 (92.9)	63 (90)
Dialysis days = 3	63 (90)	52 (74.3)	60 (85.7)	51 (72.9)	57 (81.4)	51 (72.9)	55 (78.6)	49 (70)	53 (75.7)	44 (62.9)
Non-dialysis days ≥2	66 (94.3)	66 (94.3)	65 (92.9)	66 (94.3)	63 (90)	64 (91.4)	63 (90)	62 (88.6)	61 (87.1)	59 (84.3)
Non-dialysis days ≥3	63 (90)	62 (88.6)	62 (88.6)	58 (82.9)	57 (81.4)	57 (81.4)	56 (80.0)	54 (77.1)	53 (75.7)	51 (72.9)
Non-dialysis days = 4	52 (74.3)	43 (61.4)	51 (72.9)	43 (61.4)	40 (57.1)	37 (52.9)	38 (54.3)	34 (48.9)	32 (45.7)	24 (34.3)

3.4 Discussion

3.4.1 Overview of findings

Clinical and demographic characteristics of the participants included for analysis in the present study are broadly similar to those reported for the wider Scottish HD population in the Scottish Renal Registry Report 2013. Median age was younger than the median reported for the dialysis unit (57 versus 64 years) and the Scottish HD population (SRRR 2013) but broadly similar to previous PA studies undertaken in this population (Johansen et al. 2001a; Stack and Murthy 2008; Masuda et al. 2009; Nowicki et al. 2010; Cupisti et al. 2011; Avesani et al. 2012). Diagnosed diabetics made up a slightly smaller proportion of the study sample (23%) compared that of the wider UK HD population (28%) (UKRR 2012).

This is the first study to propose minimum accelerometer wear time guidance for data reduction to enable reliable estimation of habitual PA and sedentary behaviour of people with stage 5 CKD receiving maintenance HD. Moreover, it is also the first study to recommend minimum wear times for the ActivPAL accelerometer. The principal findings are that using either the Actigraph or ActivPAL accelerometer, a minimum of one dialysis day and two non-dialysis days should provide a reliable objective estimate of habitual PA and sedentary behaviour in this sample of maintenance HD patients. A minimum of seven hours wear to define a valid day was necessary for the Actigraph while computed minimum wear for the ActivPAL indicated it was possible to include days with as little as five hours wear. Previous studies have observed that the PA of week days is more similar than when weekend PA data were added and have recommended that weekend wear should be included (Gretebeck and Montoye 1992; Ojiambo et al. 2011). However, no statistically significant difference was observed between total PA on mid-week inter-dialytic days and the two consecutive inter-dialytic days, which in other populations might normally be defined as weekend days. The recommendations here are thus made in terms of the number of dialysis and non-dialysis days required to provide reliable estimates of habitual PA.

These findings are important as seven days is a commonly prescribed monitoring period (Kristensen et al. 2010; Colley et al. 2011; Feinglass et al. 2011; Tudor-Locke et al. 2011a; Esliger et al. 2012) and a valid wear day standard of ≥10 hours has been widely adopted (Trost et al. 2005; Tudor-Locke et al. 2011a). Data reduction using these default criteria would produce extremely reliable estimates of PA and

sedentary behaviour (ICCs ranging from 0.90 to 0.94). However, the trade-off would be a catastrophic loss of data, with the exclusion of over two thirds to three quarters of participants, a scenario which is not uncommon. Colley et al. (2010) reported that application of a similarly stringent a wear criteria would have resulted in a similar level of participant exclusion (42% - 73% depending on age) from final analyses in the Canadian Health Measures Study. Importantly, the relatively high number of participants who wore their Actigraph and ActivPAL accelerometers for the prescribed seven day period (73% and 63% respectively) with the loss of four accelerometers indicates that objective measurement of habitual PA of maintenance HD patients is feasible.

3.4.2 Recommended wear time for estimation of total physical activity

The number of recommended wear days to predict total PA is in agreement with findings from previous PA reliability studies employing older uniaxial Actigraph accelerometers (Actigraph 7164 and CSA 7164). Using a lower cutpoint of >50 cpm Hart et al. (2011c) observed three days of wear were required for reliable estimates of minutes of total PA in a similar sized sample of 52 older, asymptomatic adults (69.3 ± 7.4 years) during a 21 day monitoring protocol. Three to four days and four to five days of Actigraph wear has been recommended for reliable estimation of total PA determined by a higher cutpoint (>500 cpm) in samples of apparently healthy older adults (Matthews et al. 2002) and young to middle-aged rural and urban adults (Cook and Lambert 2008). Notably, the cited studies used 12 and 10 hour daily wear thresholds respectively. The discrepancy in required wear time between this study and that of Cook and Lambert (2008) is likely mediated by the combination of a different TPA cutpoint in the cited study, and greater variability of daily PA observed in younger age groups compared to older adults. Moreover, PA of participants in the present study is effectively clamped on dialysis days with a predetermined period of inactivity and daily routine organised around HD therapy, thus limiting intra-day variability. In addition, although the cited studies employed similar if older Actigraph models, reliability analyses were performed on minutes of total PA only as opposed to normalising outcomes to wear time, which takes into account potential effects of variation in daily wear on accelerometer output.

3.4.3 Recommended wear time for estimation of sedentary behaviour

Monitor wear requirements for accurate estimation of sedentary behaviour found elsewhere in the literature contrast to the three days recommended here. Using a

higher cutpoint for sedentary behaviour (<500 cpm) Matthews et al. (2002) observed that seven days of CSA 7164 accelerometer wear were required to reliably estimate time spent sedentary in a sample of middle aged adults. Although different cutpoints for sedentary behaviour were employed by Cook and Lambert (2008) and Hart et al. (2011c) (<500 cpm and <50 cpm respectively) both studies reported five days were needed for their respective samples of young and older adults using similar uniaxial Actigraph accelerometers. Notably, a higher wear requirement of eight to nine days is recommended for similarly reliable estimates of sedentary time in children (Ojiambo et al. 2011). A possible explanation for the disparity in findings is that reliability analyses of the present study were performed on data normalised to wear time, which take into account wear time variation. Much of non-wear time is suggested to be sedentary behaviour (Tudor-Locke et al. 2011a), therefore the contrasting recommendations are likely to be mediated primarily by intra-individual variation in monitor wear relative to inter-individual variation. To support this explanation, the computed reliability coefficients for sedentary behaviour or sit/lie time in the current study were noticeably lower than other PA outcome variables (appendices XI and XII). Consequently recommended wear time for reliable estimation of minutes of time spent sedentary or seated/lying for this sample of HD patients was found to be similarly inflated at six days (minimum of eight hours wear/day) and seven days (minimum of seven hours wear/day) for Actigraph and ActivPAL accelerometers respectively (appendices XIII and XV).

3.4.4 Recommended wear time for activity counts

These data indicate that just two days wear (one dialysis and one non-dialysis) are required for reliable triaxial activity count output which provides a gross measure of all PA. Only one other wear-time reliability study was located that employed triaxial accelerometry. Using generalizability theory Coleman and Epstein (1998) found three to four days of accelerometer wear produced acceptable levels (G*>0.77 and G*>0.82 respectively) of generalisability for Tri-Trac-3D accelerometer activity count output in a sample of low-active young men. Gretebeck and Montoye (1992) simulated triaxial accelerometer output with three uniaxial Caltrac accelerometers. Spearman Brown prophecy calculations in the cited study indicated that two days wear would achieve a reliability level of 0.83 in 30 apparently healthy young men.

Overall, required wear time for acceptable triaxial activity count reliability in the present study is similar to that reported for older uniaxial Actigraph accelerometers

employed across a range of ages. Matthews et al. (2002) recommended that two to three days of wear were sufficient to provide a reliability of 0.80 for activity counts per minute in healthy adults. Similarly, Cook and Lambert (2008) and Evenson et al. (2012) reported three days of monitor wear were required for reliable uniaxial activity count output in samples of middle- and older-aged asymptomatic adults respectively. In general, greater variability of PA attributed to younger adults, and greater movement sensitivity of triaxial accelerometry may likely account for slight differences in wear time recommendations (for activity counts) with previous studies. Again, the importance of performing analyses on data normalised to account for wear time variation is underlined by large-scale accelerometer reliability studies involving children; which report similar wear time recommendations of two or three days (Rich et al. 2013 and Mattocks et al. 2008 respectively).

3.4.5 Recommended wear time for estimation of MVPA

In terms of PA that is known to provide a health enhancing effect, three days of Actigraph wear (two dialysis and one non-dialysis) are required to reliably estimate MVPA of the present sample of HD patients. This is in agreement with the results of Matthews et al. (2002) who reported three to four days of monitor wear were recommended for healthy middle aged men and women. In contrast, Cook and Lambert (2008) reported that four to five days were required to achieve acceptable reliability for MVPA in their sample of younger rural and urban adults. Required wear time appears to decrease with increasing PA intensity and advancing age with observations that MVPA is often planned and less variable in older adults (Rowe et al. 2007). Despite a similar age demographic, Hart et al. (2011c) reported that just two days of accelerometer wear were required for their sample of older adults. The discrepancy between required wear for MVPA recommended in the present study and the cited study is perhaps reconciled when taking into consideration the different daily routines unique to the HD population. An imposed medical therapy routine and commonly reported symptoms of post-dialysis fatigue potentially inhibits all PA for this population three days per week. Activities potentially denied due to the influence HD therapy such as shopping or recreational PA, are then possibly planned to be undertaken on non-dialysis days.

3.4.6 Recommended wear time for estimation of steps

The number of steps performed per day is often used as a motivational method of improving general PA levels, moreover thresholds of >9000 steps, <5000 steps, and

3500 - 5000 steps per day are associated with normal weight, obesity and chronic conditions respectively (Tudor-Locke and Myers 2001; Tudor-Locke et al. 2011a). Recommended wear time for reliable estimates of steps taken provided by either the Actigraph GT3x or ActivPAL monitors has not previously been examined. Notably, reliability for this variable was as high as other accelerometer outcomes in this study. The required wear times of three days (one dialysis and two non-dialysis days) for Actigraph and four days for ActivPAL (two dialysis and two non-dialysis days) respectively to achieve a reliability of 0.80 for this participant sample are similar to those reported in pedometer reliability studies. Three and four days of pedometer wear has been recommended for middle-aged (Tudor-Locke et al. 2005) and older adults (Hart et al. 2011c). However, just two wear days were recommended by Rowe et al. (2007) who observed with the exception of a Sunday, no significant differences in daily step counts of older adults of more advanced age (74.0 ± 9.5 years). The discrepancy in required wear compared to the present study is likely due to inter-day variance induced by the influence of HD therapy on habitual PA. In contrast Kang et al. (2009) reported five consecutive or six random days were necessary based on a year of continuous pedometry monitoring. The disparity is perhaps due to a much smaller sample (n = 23), younger participants and seasonality contributing to greater measurement variability in the cited study.

3.4.7 Defining a valid wear day and impact on participant retention

Guidance regarding hours of accelerometer wear per day is crucial in determining which days are included in any subsequent analyses. The findings of this study indicate that a minimum of seven hours wear is required to define a valid day when using the Actigraph accelerometer to estimate time in sedentary behaviour and PA. In contrast minimum wear calculations for the ActivPAL indicate that accelerometry data based on as little as four hours wear per day may be included for the characterisation of most behaviour outcomes. Applying the rubrics derived via the Spearman-Brown formula here would thus enable over 90% of the Actigraph and Activpal datasets to be included for final analyses (table 3.20).

Table 3.20 Number (and %) of participants included according to minimum daily wear time and minimum number of wear days.

Wear time criteria	**>6 hours**		**>7 hours**		**>8 hours**		**>9 hours**		**>10 hours**	
Recommended	Actigraph	Activpal	Actigraph	Activpal	Actigraph	Activpal	Actigraph	Activpal	Actigraph	Activpal
Dialysis days ≥1	70 (100)	69 (98.6)	70 (100)	69 (98.6)	**70 (100)**	**69 (98.6)**	70 (100)	68 (97.1)	70 (100)	68 (97.1)
Non-dialysis days ≥2	66 (94.3)	66 (94.3)	65 (92.9)	66 (94.3)	**63 (90)**	**64 (91.4)**	63 (90)	62 (88.6)	61 (87.1)	59 (84.3)
Participants included	66 (94.3)	66 (94.3)	65 (92.9)	66 (94.3)	**63 (90)**	**64 (91.4)**	63 (90)	61 (87.1)	61 (87.1)	59 (84.3)
Stringent	Actigraph	Activpal	Actigraph	Activpal	Actigraph	Activpal	Actigraph	Activpal	Actigraph	Activpal
Dialysis days = 3	63 (90.0)	52 (74.3)	60 (85.7)	51 (72.9)	57 (81.4)	51 (72.9)	55 (78.6)	49 (70.0)	**53 (75.7)**	**44 (62.9)**
Non-dialysis days = 4	52 (74.3)	43 (61.4)	51 (72.9)	43 (61.4)	40 (57.1)	37 (52.9)	38 (54.3)	34 (48.9)	**32 (45.7)**	**24 (34.3)**
Participants included	49 (70.0)	39 (55.7)	47 (67.1)	38 (54.3)	39 (55.7)	35 (50.0)	35 (50.0)	32 (45.7)	**29 (41.4)**	**22 (31.4)**

Minimum wear thresholds required to define a valid day in the current study contrast with several studies advocating ≥10 hours for accelerometers, a standard which has been widely employed (Troiano et al. 2008; Colley et al. 2010; Semanik et al. 2010; Tudor-Locke et al. 2011d). However, the 10 hour threshold was adopted from the research of Masse et al. (2005) who derived this benchmark from work on sample retention according to different non-wear algorithms and not reliability analyses. As Tudor-Locke et al. (2012) observed, the standard was further enshrined due to subsequent application to accelerometry data from the National Health and Nutrition Examination Study (NHANES) and inclusion into the accompanying SAS syntax.

Obviously, using a widely adopted wear criterion increases the ability to compare findings with previous health-related PA studies. However, it is important to bear in mind some of the unique characteristics of the HD population which include: high average age; high prevalence of multi-morbidity and pathology-related symptoms including fatigue; muscle weakness; shortness of breath; low motivation to engage in PA. It may be thus impractical to expect all indivduals to consistently comply with ≥10 hours day More recently, shorter wear thresholds of six to eight hours have been recommended as acceptable for preadolescents (Steele et al. 2009; Jago et al. 2010; Ojiambo et al. 2011), and overweight individuals (Chen et al. 2009).

Altering minimum wear time criteria is reported to significantly affect PA outcomes in adults (Herrmann et al. 2013; Toftager et al. 2013). However, although the influence may be less profound in low-active populations, it may still have a significant impact on sample size retention (Miller et al. 2013). Another important facet to consider is that HD therapy imposes a four-hour period of inactivity. Moreover, activity counts (for morning HD patients) during the two hours after a dialysis session are higher than the equivalent time on a non-dialysis day, comparatively lower in hours three and four post-dialysis, and not significantly different thereafter (Majchrzak et al. 2005). Therefore, including days with just four hours wear for ActivPAL would appear to be counter-intuitive when seeking to accurately characterise dialysis day PA outcomes in particular, especially if there are data from just one dialysis day available. Therefore, a higher minimum wear time threshold for both accelerometers, which balances the need for acceptable reliability while retaining a sample size that is sufficiently representative, might be more appropriate. Rich et al. (2013) reported that a wear threshold of seven to eight hours provided stable

estimates of PA in children but nonetheless recommended a higher threshold (10 hours) that both maximised reliability and sample size retention (85%).

Using the three-day standard derived in the present study and insisting on ≥10 hours wear/day advocated by Troiano et al. (2008) or the '80/70 rule' determined criterion would reduce participant data retention from 93% and 94% to 87.1% and 84% for Actigraph and ActivPAL respectively, and may introduce a source of bias into final analyses. Applying a threshold of eight hours wear would still achieve a clinically acceptable level of reliability of 0.80 with the advantage of allowing at least 90% datasets to be included for analyses regardless of accelerometer. Thus a daily wear time recommendation shorter than the widely adopted 10 hour minimum may provide an adequate balance between sufficient scientific rigour and sample size retention for this sample of stage 5 CKD HD patients. Using a similar wear criteria (four days wear with >8 hours/day) Chen et al. (2009) observed a comparable retention rate (93%) among low active participants recruited for a weight loss trial.

3.4.8 Study limitations

A limitation of this study was the moderate sample size based on self-selected volunteers drawn from a single Scottish renal dialysis unit. The average age of this participant sample was lower than the Scottish and UK HD populations (UKRR 2012; SRRR 2013). Ideally there should have been an even number of males and females to generalise findings adequately, however the sample recruited is close to the real world gender split of HD patients (UKRR 2012). Additionally, applying the target number of days derived here to all studies of PA involving HD patients will have inherent limitations. Intra-class correlation coefficients are known to be sample specific due to the magnitude of inter and intra-individual PA variability of different populations. Therefore caution should be exercised when generalising these results to the wider HD population. There are some additional limitations attached to PA data derived from accelerometry. Swimming activities are not captured and detection of non-ambulatory activities such as cycling is limited (Chen and Bassett 2005). None of the participants in this sample reported swimming activities during the study period, however three participants did report cycling as part of their weekly PA. There are limitations attached to the reliability studies performed on the ActivPAL data. Required wear for outcomes on non-dialysis days in particular increased with more stringent wear time thresholds as the sample size declined and outcome variability increased. Minimum wear recommendations for ActivPAL

outcomes on non-dialysis days are based on the assumption that had the sample size been larger the required wear would have been at least the same as that observed for the four and five hour thresholds.

3.4.9 Clinical and research implications

Accelerometer wear protocols for health-related PA studies involving HD patients have lacked uniformity and rationale, with data reduction procedures rarely stated. These data indicate that with the application of the minimum wear time recommendations reported in the current study, accelerometry data for at least 90% of participants may be retained, with a clinically acceptable level of reliability. Importantly, these findings demonstrate that missing or incomplete PA data due to variability in activity monitor wear does not necessarily mean compromised final analyses due to excessive data exclusion. Using these guidelines to assist with imputation of missing data, with either the mean observed values or one of the imputation methods suggested by Catellier et al. (2005) warrants further exploration.

Notably, these recommendations may have implications with regard to future study design such as guiding length of monitoring period to reduce participant burden. However, purposive sampling of three specific days may potentially introduce a source of bias and is suggested as an area for further research. Monitor wear guidelines presented here are recommended with the caveat that they are *minimum requirements only* in order to achieve a clinically acceptable level of reliability of 0.80. A criticism often levelled at self-report estimates of PA is that these instruments lack precision and are of limited use at an individual level (Loney et al. 2011). Accelerometry may conceivably be used in the future as an adjunct to existing routinely assessed health indices to further stratify risk and optimise health interventions for this population. It is therefore reassuring that a week of monitor wear produced reliability values for Actigraph and ActivPAL outcome variables (0.92 - 0.96 and 0.90 - 0.94 respectively when normalised to wear time) close to the reliability level of 0.95 suggested as sufficient for individual use by Nunally (1978).

A wide range of published cutpoints exist to categorise Actigraph output into sedentary behaviour or various intensities of PA, each providing substantially different estimates (Strath et al. 2003). Currently there is no consensus guidance regarding the optimal thresholds to use. Consequently, researchers face limitations when attempting meaningful and reliable synthesis of accelerometer-based PA studies. However, while cutpoints for PA and sedentary behaviour may vary, it is

clear that, when accelerometer output variables are normalised to wear time, reliability values and wear time recommendations presented in the present study are consistent with those found in the wider literature (Mattocks et al. 2008; Chen et al. 2009; Hinkley et al. 2012; Rich et al. 2013). Lastly, seasonality, which is reported to affect accelerometer output reliability in postal workers (Washburn et al. 1989) and children (Corder et al. 2008) was not investigated in this sample and is suggested as an area of further research in the stage 5 CKD HD population.

3.5 Conclusion

Accelerometry is increasingly being adopted to monitor PA behaviour and examine mechanisms of PA-mediated health outcomes in the HD population. Guidelines regarding accelerometer data capture and reduction are therefore important to ensure that derived PA outcome variables are reliable. Recommended accelerometer wear times vary according to different PA outcomes. However, regardless of whether Actigraph or ActivPAL accelerometers are employed, data from one dialysis day and two non-dialysis days should be sufficient to yield reliable estimates of total PA and sedentary behaviour in comparable stage 5 CKD HD patients. Although inclusion of accelerometry data with as few as four hours of monitor wear does not appear to adversely impact reliability of some PA outcomes, a minimum of eight hours wear is deemed more appropriate. These recommendations reconcile the tension between sufficient measurement rigour and retention of a meaningful sample size for final analyses. It is emphasised that stated wear time recommendations are a minimum requirement only, to achieve a clinically acceptable level of reliability for PA outcomes, and that reliability sufficient for use at an individual level will more likely be realised from a seven day wear protocol.

What is known about this topic:

- Participant mounted accelerometers are increasingly being employed for physical activity surveillance in health-based studies.
- Accelerometer wear time guidelines are available for children and asymptomatic adults.

What this study adds:

- Clear recommendations pertaining to methodological considerations regarding the use of accelerometers employed for estimating physical activity and sedentary behaviour of people receiving HD therapy for stage 5 CKD.

Chapter 4: Concordance of physical activity methods

4.1 Introduction

Questionnaires have commonly been employed to characterise PA of people receiving HD with more than two thirds of published studies using a range of self-report methods. Notably, large-scale epidemiological studies have demonstrated that a single question regarding exercise frequency is predictive of mortality in the haemodialysis (HD) population (O'Hare et al. 2003; Tentori et al. 2010). However, objective methods of PA assessment have enabled deeper insights into patterns of PA (Majchrzak et al. 2005), and have contributed the majority of what is known regarding relationships between PA levels and traditional CVD risk factors in the HD population. For example, indices of PA estimated by pedometers and accelerometers are inversely associated with BMI, cholesterol, triglycerides, inflammation and diabetes (Majchrzak et al. 2005; Zamojska et al. 2006; Masuda et al. 2009; Nowicki et al. 2010; Mafra et al. 2011; Avesani et al. 2012). In addition, findings from HD health studies show accelerometer derived PA outcomes are associated with markers of health status such as nutrition (Johansen et al. 2000; Zamojska et al. 2006; Cupisti et al. 2011) and bone mineral density (Ota et al. 1997). Intuitively, PA underpins aspects of physical function such as gait speed of HD patients (Johansen et al. 2001a; Masuda et al. 2009), which is also predictive of mortality risk (Afilalo et al. 2010).

While research into PA mediated health benefits for people with stage 5 CKD has become more sophisticated there is no uniformity regarding assessment methods employed. Moreover, despite the number of studies undertaken in uraemia, which include PA outcomes, there is a paucity of studies examining concordance of diverse assessment methods employed, collectively limiting direct comparisons and synthesis of study findings. The only study comparing PA assessment methods reported a moderate association ($r = 0.59$, $p < 0.001$) between total daily energy expenditure (EE) estimated from the Stanford Seven-Day Recall (7DR) questionnaire and accelerometer activity counts (Johansen et al. 2001b). However, level of agreement between meaningful outcomes such as volume of PA associated with a health enhancing effect was not undertaken to establish whether objective and subjective estiamtes could be used interchangeably in this population.

A shortcoming of health studies in the stage 5 CKD population that have employed PA questionnaires, has been their inability to accurately quantify participants'

sedentary behaviour. Participants have instead been categorised as sedentary according to predefined criteria (ie; less than one exercise bout per week, or tertile splits). This is important as sedentary behaviour is now defined as any waking behaviour characterized by an energy expenditure of ≤1.5 metabolic equivalents (METs) while in a sitting or reclining posture (SBRN 2012). Crucially, accelerometers are able to capture patterns of inactivity in a way that current self-report methods are not able to replicate (Pate et al. 2008; Celis-Morales et al. 2012; Clark et al. 2009).

4.1.1 Accelerometer estimation of activity and sedentary behaviour

Of the motion sensors currently available only the ActivPAL and Actigraph accelerometers have the ability to characterise sedentary behaviour. Data from PA studies using the latter have already demonstrated important associations between objectively measured sedentary behaviour and cardiometabolic risk in the general population (Healy et al. 2008a, Healy et al. 2008b). The Actigraph (Pensacola, Florida, USA) family of monitors (7164, GT1M, GT3x) convert body motion into activity counts and use an activity count cutpoint to categorise PA and sedentary behaviour. Notably these monitors have been used in large epidemiological studies such as NHANES (Matthews et al. 2008) and research exploring the adverse health effects of sedentary behaviour (Healy et al. 2008a; Healy et al. 2008b). The ActivPAL (PAL Technologies Ltd, Glasgow) is a more recently developed accelerometer which employs inclinometry to monitor time spent seated/lying (sedentary) or in standing activities (physical activity) and postural transitions (sit-to-stand).

Concordance of ActivPAL and Actigraph estimates of sedentary behaviour and total PA has been evaluated in samples of pre-schoolers (Martin et al. 2011), school children (Ridgers et al. 2012), adolescents (Matthews et al. 2013), and a wide age range of adults (Hart et al. 2011c; Kozey-Keadle et al. 2011; Lyden et al. 2012; Clemes et al. 2012). Findings vary regarding the level of agreement between these devices, with little uniformity of Actigraph cutpoints employed (range <50 to <1100 cpm), due in part to differing definitions of sedentary behaviour, some of which include silent standing (Martin et al. 2011). Moreover, previous studies have predominantly been conducted in apparently healthy individuals. As yet no studies involving people with long-term conditions such as stage 5 CKD have examined whether similar outcomes from these monitors agree closely enough to be used

interchangeably. In addition, an advantage of the Actigraph is that it is able to categorise activity counts into levels of PA intensity. Activity count output from the ActivPAL is not currently utilised but if outcome agreement were acceptable, established Actigraph based cutpoints for categorising PA intensity may theoretically be employed for this monitor.

4.1.2 Summary

Physical activity is implicated in numerous health outcomes of people receiving HD for stage 5 CKD. Clearly, accurate assessment of PA is indicated in the HD population to examine PA mediated mechanisms of health and to identify those at risk of poor outcomes. Currently there is no standardised approach to characterising habitual PA of the HD population. Moreover, accumulating evidence regarding the adverse health effects of sedentary behaviour indicates that objective monitoring of this outcome should be undertaken to complement PA health research and interventions. Therefore there is a need to examine the level of agreement between of accelerometers capable of estimating both sedentary behaviour and PA outcomes in the HD population to assist with standardisation of assessment methods. In addition, there is a large amount of PA data pertaining to the stage 5 CKD HD population that has already been collected using self-report. It would be advantageous to determine whether subjective estimates of PA agree closely enough with accelerometry to enable pooling of results.

The objectives of this study were to:

- To examine the concordance of subjective (Stanford 7 Day Recall questionnaire) and objective (Actigraph GT3X) methods of estimating physical activity of people with stage 5 CKD.
- To examine the concordance of Actigraph GT3X and ActivPAL estimates of sedentary behaviour and similar PA outcomes of people with stage 5 CKD.
- To examine the concordance of subjective and objective estimates of energy expenditure derived from the Stanford 7 Day Recall, Actigraph GT3X and ActivPAL.

4.2 Methods

4.2.1 Study design and participant recruitment

The present study was conformed to the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the West of Scotland Research Ethics Committee and the Monklands Hospital Research and Development Department. This was a concordance study involving a cohort of 73 self-selected volunteer participants undergoing maintenance HD therapy for stage 5 CKD recruited from an NHS outpatient HD unit at Monklands Hospital, Airdrie. Written informed consent was obtained from each participant prior to study commencement.

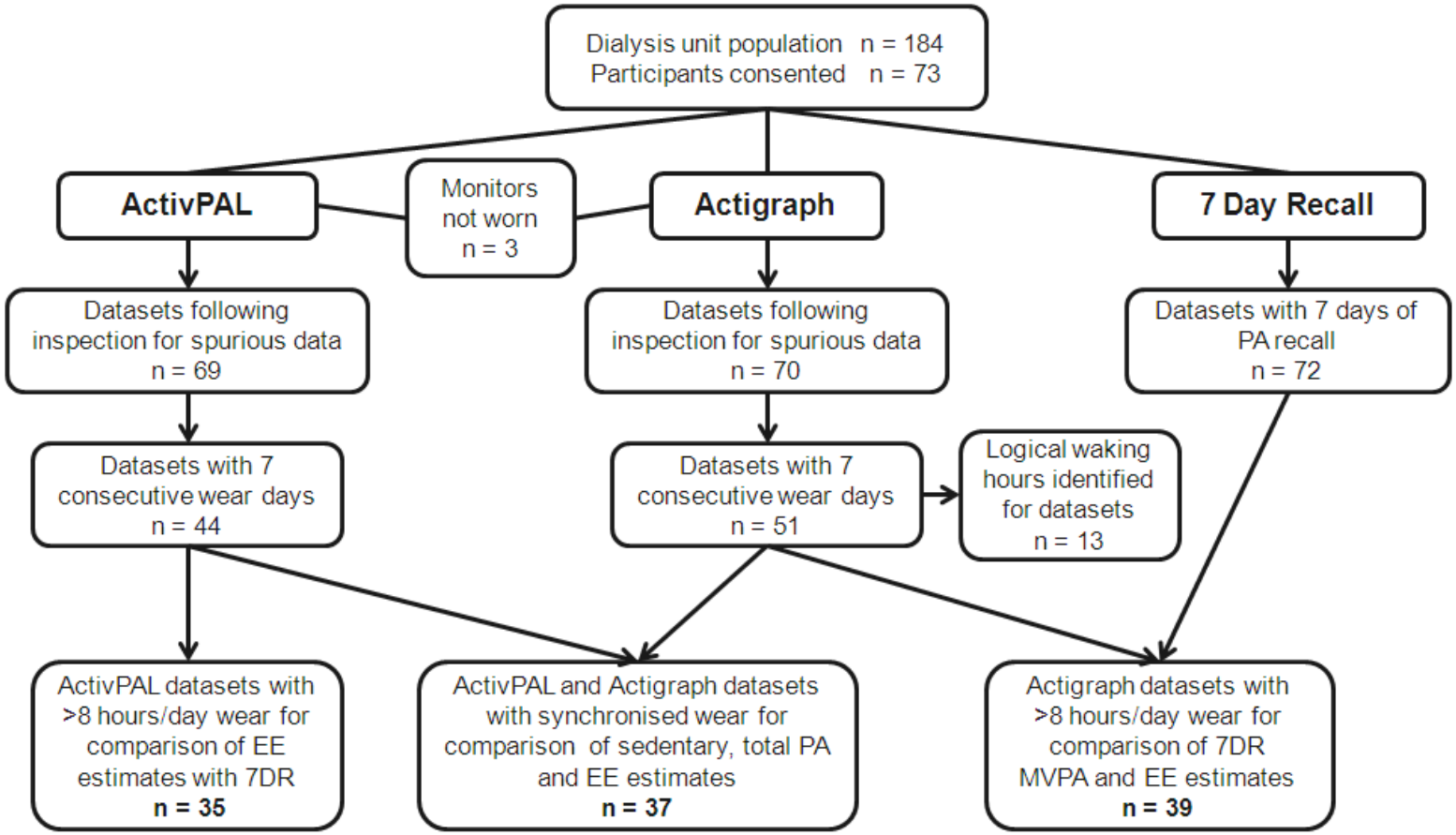
4.2.2 Subjective and objective estimation of physical activity outcomes

Physical activity data of the participants in this study was collected between November 2011 and August 2013. This comprised, for each patient, the concurrent acquisition of PA behaviour data obtained objectively via Actigraph GT3X (Actigraph Corp, Pensacola, Florida) and ActivPal (PAL Technologies Ltd, Glasgow) accelerometers and subjectively using the Stanford 7-day recall (7DR) questionnaire (Sallis et al. 1985). The ActivPAL and Actigraph accelerometers were synchronised and configured to collect data over 15 second epochs (McClain et al. 2008) using the proprietary software for each accelerometer installed on the same PC laptop. The accelerometers were worn as per general methods sections 2.5.4 and 2.5.8 during waking hours, which was recorded via a monitor wear log (appendices Va and Vb). Both acelerometers were retrieved from participants on day nine coinciding with a routine HD appointment and data were downloaded using the proprietary Actilife and ActivPAL software. The 7DR was also administered on this day as per general methods section 2.5.9.

4.2.3 Data cleaning for Actigraph and ActivPAL accelerometers

Data cleaning of Actigraph GT3X and ActivPAL was undertaken as per general methods sections 2.5.3 to 2.5.8. ActivPAL and Actigraph wear times were checked for agreement to enable accurate comparison of shared outcomes. Where a difference in monitor wear times was observed, the on or off time was adjusted to ensure the wear period for both accelerometers was synchronised. Only participants with seven days of accelerometer data and a minimum of eight hours wear/day were included for concordance analyses with the 7DR. Figure 4.1 describes the data cleaning and inclusion process for 7DR, Actigraph GT3x and ActivPAL PA data.

Figure 4.1 Flowchart of patient participation, accelerometer data cleaning, and data inclusion for concordance analyses.



4.2.4 Categorisation physical activity outcome variables

Similar Actigraph and ActivPAL outcomes were categorised as per section 3.4.5 in chapter three. Subjective estimates of PA obtained via the 7DR (Blair et al. 1985) were collated according to the standardised script (Sallis et al. 1985) accompanying the questionnaire (appendix VI b). Self-report information regarding the dimensions of participants' PA such as frequency, duration and intensity were used to derive an energy expenditure (EE) value for the seven-day monitoring period to be compared with ActivPAL and Actigraph estimates. The physiological cost of PA categorised as moderate to very hard intensity was assigned using the Compendium of Physical Activities (Ainsworth et al. 2011). Energy expenditure was subsequently calculated using the duration of the activity as per equation 4.1 (Ainsworth et al. 2000).

Equation 4.1 Seven Day Recall EE for moderate to very hard PA
Physiological cost of activity (METs) x activity duration (minutes) = EE (MET minutes)

4.2.5 Energy expenditure output comparisons

A direct comparison between the EE estimations of each method is made challenging due to the idiosyncratic way each instrument derives its EE value. The Actilife software estimates EE for the Actigraph from moderate to vigorous physical activity (MVPA) using the Freedson et al. (1998) equation (equation 4.2) in kilocalories (kcals). The 7DR also derives EE from MVPA and although the most straightforward calculation is for MET minutes (equation 4.1) an outcome value in kcals may also be calculated (equation 4.3).

Equation 4.2 Actilife EE calculation for moderate to vigorous PA

If CPM > 1951 then:

$$kcals/min = Scale \times (0.00094 \times CPM + (0.1346 \times BM - 7.37418))$$

where:

CPM = Counts per minute
BM = Body mass in kg

(Freedson et al. 1998)

Equation 4.3 Calculation of kcals from 7 Day Recall questionnaire MVPA

kcals/min = Activity MET value x 3.5 x body weight (kg) / 200

EE (kcals) = kcals/min x Activity duration

(Ainsworth et al. 2000)

The ActivPAL provides an EE value in MET minutes calculated from total wear time which includes sedentary as well as active periods. The 7DR also provides an EE estimate in MET minutes but only for bouts of MVPA which meet a minimum threshold of 10 minutes. In order to compare 7DR and ActivPAL EE outcome values, EE from MVPA (equation 4.1) was added to EE derived from estimated time in light PA (equation 4.4) using the 1.5 MET threshold (Pate et al. 1996; Leenders et al. 2000). In order to account for time spent sedentary during HD therapy, four hours of sedentary EE (one sedentary minute = 1 MET min) (Leenders et al. 2000) were substituted in for time otherwise defined as light PA on the three dialysis days.

Equation 4.4 Seven Day Recall waking hour EE (MET minutes)

Dialysis Day Total MET mins = (MVPA METmins) + 1.5 x (Light PA mins – 240) + 240

Non-Dialysis Day Total MET mins = (MVPA METmins) + 1.5 x Light PA mins

In order to achieve a direct comparison between ActivPAL and Actigraph estimates of EE for the same period of wear an EE value including light PA and sedentary time had to be calculated for the latter. An Actilife software option allows the combined use of the Freedson et al. (1998) equation and the Williams Work Energy equation (Williams 1998) to estimate EE from all PA recorded by the Actigraph (equation 4.5).

Equation 4.5 Actigraph total PA EE

If CPM > 1951 then:

$$kcals/min = Scale \times (0.00094 \times CPM + (0.1346 \times BM - 7.37418))$$

If CPM < 1951 then:

$$kcals/min = CPM \times 0.0000191 \times BM$$

where:

CPM = Counts per minute

BM = Body mass in kg

(Williams 1998)

To compare ActivPAL and Actigraph EE estimates in the same units the Ainsworth et al. (2000) equation for converting METs into kcals/min (equation 4.3) was adapted to convert Actigraph kcals/min into METs (equation 4.6). The MET value was then multiplied by the number of Actigraph categorised light to vigorous PA minutes. This

value was added to the resting metabolic equivalents for each minute of Actigraph defined sedentary time (one sedentary minute = 1 MET minute) to derive total EE in MET minutes for Actigraph monitor wear time.

Equation 4.6 Actigraph physical activity kcal conversion to MET minutes

((Actigraph PA kcals / total PA minutes) x 200) / body mass) / 3.5 = METs/minute

4.2.6 Data Analysis

The following Actigraph derived outcome variables are reported as daily averages for the seven day study period: sedentary time, total PA, moderate to vigorous PA (MVPA), step counts, uniaxial activity counts and energy expenditure. Seven day averages of the outcomes for the ActivPAL are: sit/lie time, stand time, step counts, uniaxial activity counts and energy expenditure. All PA indices obtained via accelerometry were also normalised to wear time to adjust for intra and inter-individual variation in monitor wear (Hinkley et al. 2012). Normality testing of PA outcome variables was undertaken using a Shapiro-Wilk as the sample was less than 50 participants. Outcomes were reported as mean values and standard deviation (SD) for parametric variables or median values and interquartile range(IQR) for non-normally distributed data.

Table 4.1 Similar outcome variables for objective and subjective PA assessment methods.

Activpal	Actigraph	Seven Day Recall
Sit/Lie time	Sedentary time	
	Light Activity Moderate Activity Vigorous Activity Very Vigorous Activity	Light Activity Moderate Activity Hard Activity Very Hard Activity
Total standing time	Total physical activity	
Activity Counts	Activity Counts	
Step counts	Step counts	
Energy Expenditure	Energy Expenditure	Energy Expenditure

Agreement of similar outcome variables from each PA instrument illustrated in table 4.1 was assessed using the following three statistical approaches: correlational analysis, Bland-Altman analysis, tests for significant outcome value differences. Although correlational analysis provides an indication of the strength of the linear relationship of two variables it does not reflect systematic differences and whether the instruments from which the outcomes were derived may be used interchangeably (Oliver et al. 2007). Therefore, Bland-Altman analysis was undertaken to calculate the 95% limits of agreement (LOA) (1.96 times the standard deviation of the differences) (Bland and Altman 1986). Although this technique is not a statistical test, it provides an indication of the relative measurement bias between the assessment tools. Moreover, if the differences between the measures lie within LOA that are clinically important, the two methods may be used interchangeably (Bland and Altman 1986). Bland-Altman plots were also examined for proportional bias between the two methods by regressing the outcome value differences with the averages. A relationship indicating the existence of proportional bias indicates that the methods do not agree equally through the range of measurements (i.e. the limits of agreement will depend on the actual measurement). Bland and Altman (1986) also suggest that when a relationship between the differences and averages of the two measures is found in the form of a significant regression line slope, that the regression-based 95% limits of agreement should be provided. Finally, a paired t-test or Wilcoxon signed-rank test (non-parametric equivalent) was employed (depending on outcome variable distribution) to determine whether there was a significant difference in shared outcome values.

4.3 Results

4.3.1 Physical activity assessment compliance

Participants with seven consecutive days of data for each PA assessment method were included for analyses. Of the 70 participants who took part and wore the accelerometers, 7DR derived subjective estimates of PA were obtained for 69 individuals. One person was unable to recall PA for more than two days of the study period. Accelerometer wear compliance over the seven day study period was greater for Actigraph (n = 51, 73%) compared to ActivPAL (n = 44, 63%). The number of participants (with seven days of PA data for both accelerometers) retained for concordance analyses of ActivPAL and Actigraph outcomes (was reduced to just over

half the recruited sample (n = 37) due to instances of participants wearing one or other of the monitors for fewer than seven days (figure 4.1). Figure 4.1 shows the sample differed slightly for analyses of shared outcomes between the Actigraph and 7DR (n = 39) and ActivPAL and 7DR (n = 35).

4.3.2 Participant descriptives

The reader is referred to table 3.2 in chapter 3 for a full descriptive presentation of demographic and clinical characteristics of the 70 participants who took part in this study. Overall, clinical characteristics of the participants included for analyses were similar to the initially recruited (larger) sample (table 4.2). Average age was slightly higher but range remained the same (25 to 87 years). In addition there was a lower percentage of female participants, and HD vintage was older.

Table 4.2 Demographic and clinical characteristics of the total study sample and by PA assessment method concordance subgroup.

	Total Sample	**7 DR / Actigraph**	**ActivPAL / Actigraph**	**7DR / ActivPAL**
n = (M / F %)	70 (66/34)	39 (72/28)	37 (78/22)	35 (80/20)
Diabetes	16 (23%)	10 (26%)	8 (22%)	7 (20%)
Age (years)	55.9 ± 15.7	58.4 ± 16.1	57.7 ± 16.0	59.9 ± 16.2
BMI (kg/m^2)	27.7 (24.3 - 31.7)	29.2 (24.9 - 31.8)	28.3 (± 4.5)	28.3 ± 4.5
Albumin (g/L)	39.0 (36.0 - 42.0)	39.0 (36.0 - 41.0)	39.0 (36.0 - 41.0)	39.0 (36.0 - 41.0)
Hb (g/dL)	11.3 ± 1.0	11.5 ± 0.8	11.4 ± 0.9	11.5 ± 0.8
HD adequacy (%)	71 (66 - 75)	71 (66 - 75)	72 (67 - 74)	71.0 (66.0 - 74.0)
HD vintage (mths)	15.8 (6.8 - 32.0)	19.3 (9.2 - 37.3)	19.3 (9.1 - 42.0)	17.5 (9.2 - 37.3)

A Shapiro-Wilks test indicated all 7DR outcome variables except calculated light PA were non-normally distributed (appendix XVIII). Accelerometer outcome variables were non-normally distributed except for ActivPAL sit/lie minutes and Actigraph sedentary minutes. Descriptive statistics for sedentary behaviour and PA outcomes obtained from each PA assessment method are presented in table 4.3.

Table 4.3 Accelerometer and 7 DR derived (daily average) estimates of PA and sedentary behaviour outcomes for people with stage 5 CKD [normally distributed data are reported as mean ± SD and non-normally distributed data as median (IQR)].

Outcome	ActivPAL	Actigraph	Seven Day recall
Sedentary (min) Sedentary (%)	592.9 ± 108.4 78.1 (71.7 - 84.5)	610.1 ± 118.2 78.6 (73.4 - 86.9)	
Light PA (min)		115.9 ± 57.8 [††] 108.1 (78.5 - 139.4)	863.9 ± 96.4 822.9 (786.4 - 887.9) [†]
Moderate PA (min)		8.1 (1.9 - 20.6)	22.1 (5.4 - 63.2)
Vigorous PA (min)		0.04 (0.0 - 0.1)	0
MVPA (min)		8.1 (2.0 - 20.9)	22.1 (6.4 - 63.2)
Total PA (min) Total PA (%)	171.8 (109.5 - 235.9) 21.9 (15.5 - 28.4)	159.1 (108.2 - 224.9) 21.4 (13.1 - 26.6)	
Steps / day Steps / minute	3103 (1703 - 4643) 4.1 (2.3 - 6.4)	2931 (1295 - 4407) 3.9 (1.8 - 5.7)	
Counts/day Counts/min	632636 (288660 - 1043874) 803 (433 - 1301)	100162 (41002 - 142092) 128 (51 - 180)	
EE (kcals)		12.0 (4.0 - 78.3)	108.7 (36.8 - 376.6)
EE (MET mins)	1144.1 ± 150.6 1145.0 (1030.2 - 1290.7) [§]		1331.2 ± 177.0 [†¥] 1333.9 (1270.7 - 1455.0) [¥]
EE (MET mins)	1093.8 ± 190.3	780.6 ± 131.3	

[§] Variable normally distributed. Median (IQR) reported for comparison purposes.

[†] Variable not normally distributed. Mean (±SD) reported for comparison purposes.

[¥] Adjusted 'total day' energy expenditure

Table 4.4 summarises the results of statistical testing for differences between similar outcomes from each PA assessment method. A paired t-test revealed Actigraph and ActivPAL estimated sedentary minutes were significantly different, while a Wilcoxon signed-rank test found no significant difference as a percentage of monitor wear time. No significant differences were observed between Actigraph and ActivPAL estimates of time in total PA (both minutes/day and as a percentage of wear time) using the Wilcoxon signed-rank test. A paired t-test revealed a significant difference between ActivPAL and Actigraph estimated EE. Non-parametric tests of differences for the remaining non-normally distributed accelerometer outcomes showed step count estimates (per day and per minute of monitor wear time), uniaxial activity counts output (per day and per minute) and EE were significantly different. A significant difference was observed between all shared PA intensity categories estimated subjectively by the 7DR and objectively by the Actigraph, as well as the collapsed category of MVPA.

Subjective and objective estimates of EE derived via the ActivPAL and 7DR questionnaire respectively also exhibited a significant difference. In general effect sizes for all observed differences between PA assessment methods were large except for ActivPAL and Actigraph estimated minutes of sedentary time, which was small.

Table 4.4 Results of statistical testing for differences between similar outcome variables of different physical activity assessment methods.

<table>
<tr><th>Activity variable</th><th>ActivPAL</th><th>Actigraph</th><th>Seven Day Recall</th></tr>
<tr><td>Sedentary (min)
Sedentary (%)</td><td colspan="2">(36) t = -2.277 p = 0.029, d = 0.38
Z = -1.098 p = 0.056</td><td></td></tr>
<tr><td>Light PA</td><td rowspan="4"></td><td colspan="2">(38) t = 44.14 p < 0.001, d = 14.14</td></tr>
<tr><td>Moderate PA</td><td colspan="2">Z = -5.196 p < 0.001, r = 0.83</td></tr>
<tr><td>Vigorous PA</td><td colspan="2">Z = -4.142 p < 0.001, r = 0.66</td></tr>
<tr><td>MVPA</td><td colspan="2">Z = -4.605 p < 0.001, r = 0.74</td></tr>
<tr><td>Total PA (min)
Total PA (%)</td><td colspan="2">Z = -1.924 p = 0.054
Z = -1.908 p = 0.056</td><td></td></tr>
<tr><td>Steps/day
Steps/min</td><td colspan="2">Z = -4.594 p < 0.001, r = 0.76
Z = -4.376 p < 0.001, r = 0.72</td><td></td></tr>
<tr><td>Activity counts/day
Activity counts/min</td><td colspan="2">Z = -5.303 p < 0.001, r = 0.87
Z = -5.303 p < 0.001, r = 0.87</td><td></td></tr>
<tr><td rowspan="3">Energy Expenditure</td><td colspan="2">(36) t = 25.096, p < 0.001, d = 4.1</td><td></td></tr>
<tr><td></td><td colspan="2">Z = -4.865, p < 0.001, r = 0.78</td></tr>
<tr><td colspan="3">(35) t = 8.7, p < 0.001, d = 1.47</td></tr>
</table>

4.3.3 Concordance of Actigraph and ActivPAL outcome variables

Figures 4.2 and 4.3 show a strong relationship between ActivPAL and Actigraph estimates of minutes spent sedentary (Pearson's r = 0.92, p < 0.001) and as a percentage of wear time (Spearman's rho = 0.81, p < 0.001). The relationship remained the same for sedentary minutes on dialysis days (r = 0.92, p < 0.001) and non-dialysis days (Pearson's r = 0.93, p < 0.001) when the data were plotted according to the different conditions (appendices XIX a and XIX c). The correlation for sedentary behaviour percentage as a percentage of wear time was slightly weaker on dialysis days compared to non-dialysis days (Spearman's rho = 0.77, p < 0.001 versus 0.81, p < 0.001 respectively) (appendices XIX g and XIX i).

Figure 4.2 Actigraph versus ActivPAL estimated sedentary time (mins).

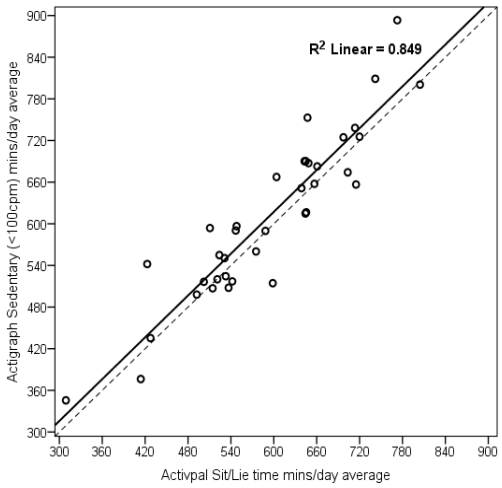
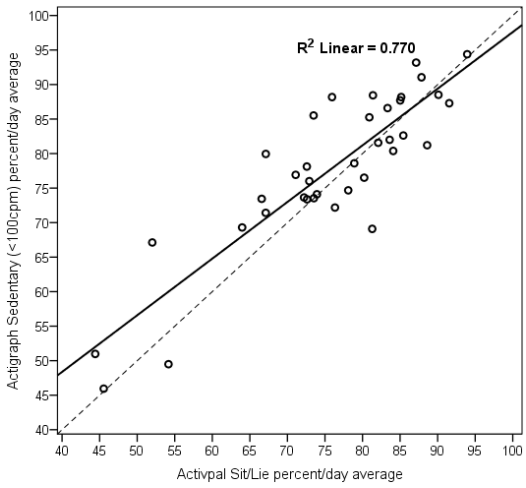


Figure 4.3 Actigraph versus ActivPAL estimated sedentary time (% of wear).



Bland-Altman analysis shows Actigraph estimated more minutes of sedentary time (figure 4.4) with a mean bias of +17.2 minutes (LOA: +107.1 mins to -72.8 mins). Mean bias on dialysis days was lower at +6.4 minutes (LOA: +98.1, -85.4), and higher on non-dialysis days (+25.3 minutes, LOA: +123.6, -73.0) (Appendices XIX b and XIX d). Bland-Altman analysis of estimated sedentary behaviour as a percentage of wear time, showed a mean daily bias of + 2.0% (LOA: +13.3, -9.4%) for Actigraph over ActivPAL (figure 4.5). On dialysis days the mean bias was lower at 0.4% (LOA: +11.4, -10.4) and higher on non-dialysis days at 3.7 % (LOA: +17.2, -9.8) (appendices XIX f and XIX h).

Figure 4.4 Bland-Altman plot Actigraph and ActivPAL sedentary time (mins/day).

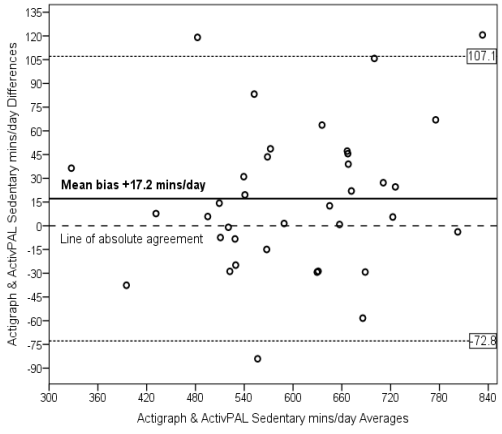
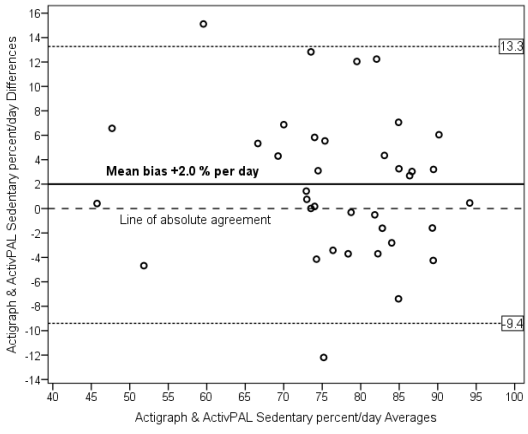


Figure 4.5 Bland-Altman plot Actigraph and ActivPAL sedentary time (% wear).



Figures 4.6 and 4.7 show ActivPAL estimated standing time correlated strongly with Actigraph estimated minutes of total PA (Spearman's rho = 0.84, p < 0.001) and as a percentage of wear time (Spearman's rho = 0.81, p < 0.001) respectively. Associations for minutes of standing and total PA were stronger on non-dialysis days compared to dialysis days (Pearson's r = 0.88 and Spearman's rho = 0.83, p < 0.001 respectively) (appendices XIX i and XIX k). As a percentage of wear time the correlations were also slightly stronger on non-dialysis days compared to dialysis days (Spearman's rho = 0.83 and 0.78, p < 0.001 respectively) (appendices XIX m and XIX o).

Figure 4.6 Actigraph versus ActivPAL estimated total PA (mins/day).

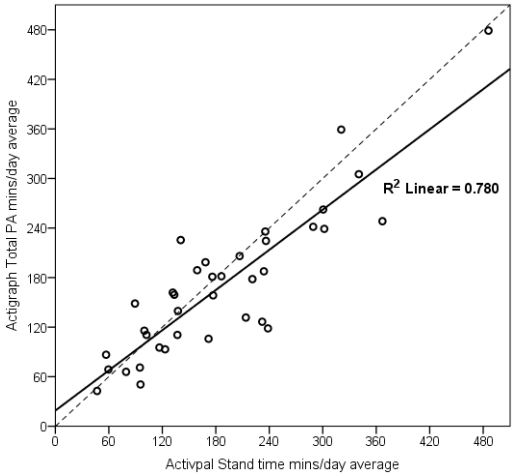


Figure 4.7 Actigraph versus ActivPAL estimated total PA (% wear).

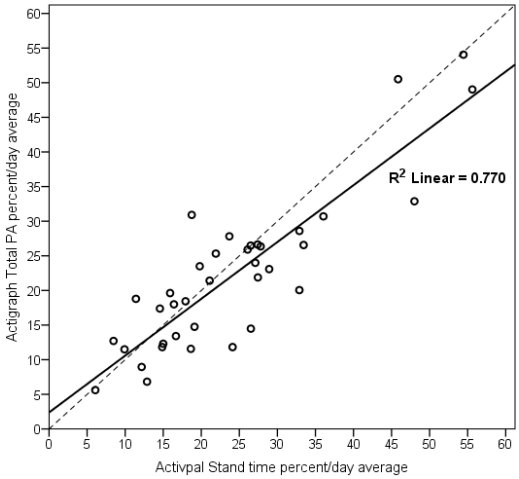


Figure 4.8 Bland-Altman plot Actigraph and ActivPAL total PA (mins/day).

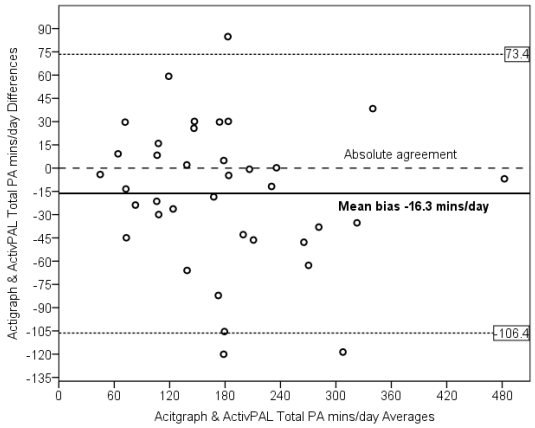


Figure 4.9 Bland-Altman plot Actigraph and ActivPAL total PA (% day).

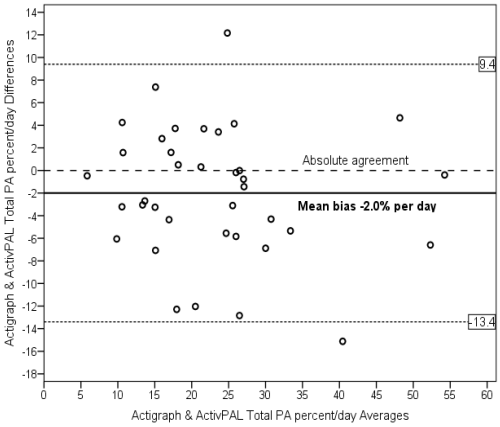


Figure 4.8 shows the Actigraph estimated fewer minutes in total PA with a mean daily bias of -16.3 minutes (+73.4, -106.4). When normalised to wear time (figure 4.9) this difference translated to a mean bias of -2.0% (LOA: +9.4, -13.4). The systematic bias was lower on dialysis days compared to non-dialysis days (appendices XIX j and XIX l) for both minutes of total PA (-5.5 minutes, LOA: 86.4, -97.4 versus -24.4 minutes, LOA: 73.9, -122.8) and as a percentage of wear time (-0.6%, LOA: 10.4, – 11.6 versus -3.0%, LOA: 10.3, -16.4) (appendices XIX n and XIX p).

Figure 4.10 Actigraph versus ActivPAL estimated steps/day.

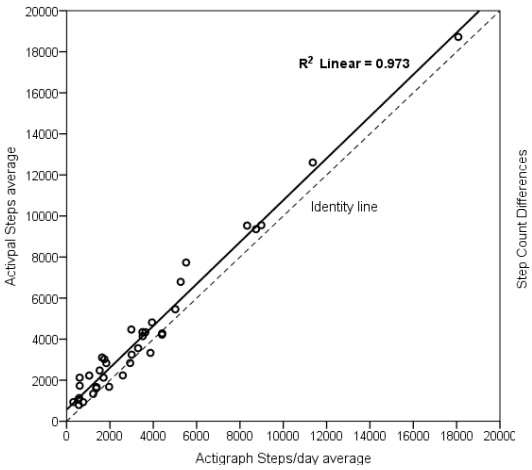
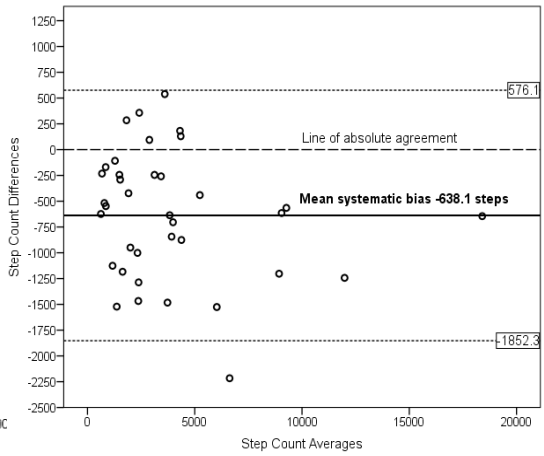


Figure 4.11 Bland-Altman plot Actigraph and ActivPAL estimated steps/day.



ActivPAL and Actigraph estimated steps/day correlated strongly (Spearman's rho = 0.95, p < 0.001) (figure 4.10) and remained similarly strong on dialysis days (Spearman's rho = 0.89, p < 0.001) and non-dialysis days (Spearman's rho = 0.94, p < 0.001) (appendices XX a and XX c). Bland-Altman analysis shows fewer steps/day estimated by Actigraph compared to ActivPAL (figure 4.11) with a substantial mean bias of -638 steps/day (LOA: +576, -1852). Mean bias was lower on dialysis days (-422 steps) with narrower limits of agreement (+615, -1458) and higher on non-dialysis days (-800 steps, LOA: +655, -2255) (appendices XX b and XX d).

Non-parametric analysis revealed average daily uniaxial activity counts recorded by ActivPAL were strongly correlated with Actigraph counts (figure 4.12) (Spearman's rho = 0.95, p < 0.001). Relationships between the two accelerometers for uniaxial activity count output remained similarly strong on dialysis (rho = 0.93, p < 0.001) and non-

dialysis days (rho = 0.93, p < 0.001) (appendices XX e and XX g). The Bland-Altman plot (figure 4.13) shows ActivPAL recorded more uniaxial activity counts compared to the Actigraph (mean bias +701,193 counts/day, LOA: 196,4879, -562,493). The disparity between the accelerometers increased proportionally (Spearman's rho = 0.99, p < 0.001) with greater volume of PA. Mean bias on dialysis days was lower (+593,986 counts/day, LOA: +1,220,442, -32,471) and higher on non-dialysis days (+781,598 counts/day, LOA: 2,152,418, -589,221) (appendices XX f and XX h). However, the same linear increase in activity count differences was observed for both conditions

Figure 4.12 Actigraph versus ActivPAL uniaxial activity counts/day.

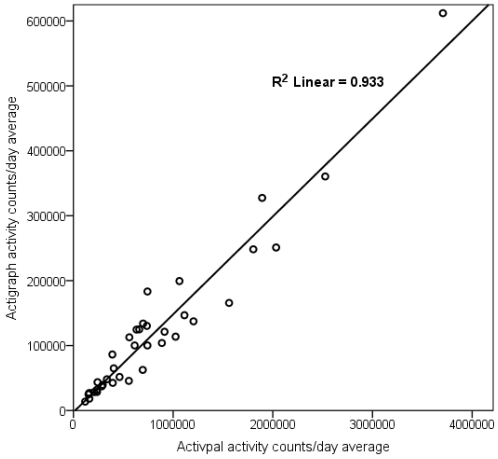
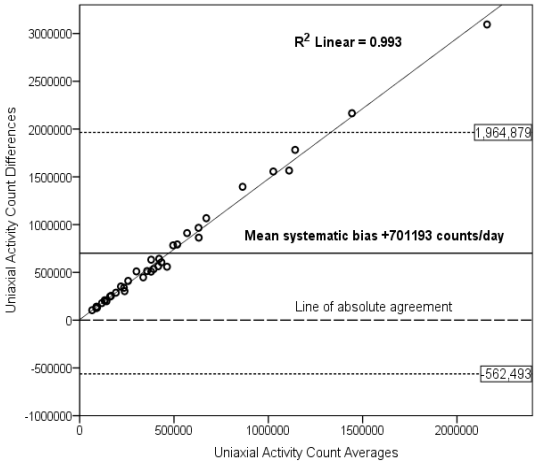


Figure 4.13 Bland-Altman plot Actigraph and ActivPAL uniaxial activity counts/day.



When ActivPAL and Actigraph activity counts were normalised to wear time as counts per minute (cpm) the correlation was similar to that observed for average daily activity counts (Spearman's rho = 0.94, p < 0.001) (figure 4.14). The association between the two accelerometers for this outcome remained similarly strong on dialysis (rho = 0.92, p < 0.001) and non-dialysis days (rho = 0.92, p < 0.001) (appendices XX i and XX k). Bland-Altman analysis (4.15) shows that the ActivPAL registered more activity counts per minute compared to the Actigraph with a mean daily bias of +913 counts/min (95% LOA = +2,520, -694). As with activity counts per day, the difference in counts per minute increased in a linear fashion (Spearman's rho = 0.99, p < 0.001) as average volume of PA measured increased. On dialysis days the mean bias was +676 counts/day (LOA: +1,876, -523) while on non-dialysis days it was +1,090 counts/day

(LOA: 3,091, -909). The same linear increase in activity counts/min was observed on both dialysis and non-dialysis days (appendices XX j and XX l).

Figure 4.14 Actigraph versus ActivPAL uniaxial counts/min.

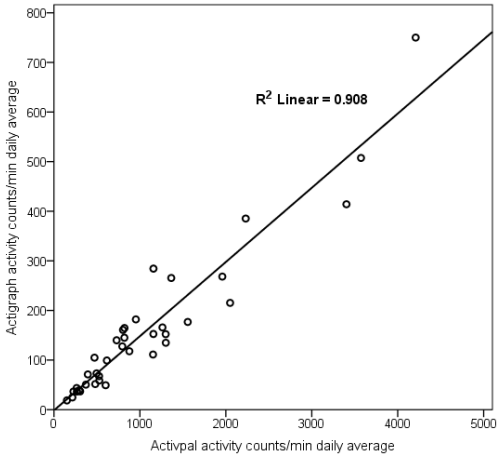
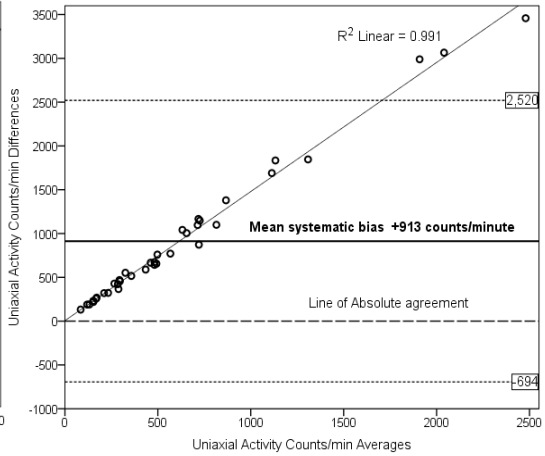


Figure 4.15 Bland-Altman plot Actigraph and ActivPAL uniaxial counts/min.



4.3.4 Concordance of the 7-day Recall questionnaire and Actigraph

No relationship was observed ($p > 0.05$) between 7DR questionnaire and the Actigraph accelerometer for estimated light PA. Mean daily values for 7DR and Actigraph estimates of light PA were 863.9 ± 96.4 and 115.9 ± 57.8 minutes respectively resulting in a large significant difference between these two assessment methods (table 4.4). No further analysis was undertaken for this outcome.

Figure 4.16 7DR versus Actigraph estimated MVPA mins/day.

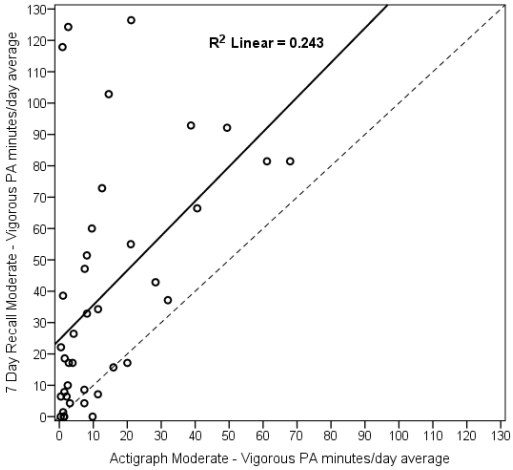


Figure 4.17 Bland-Altman plot 7DR and Actigraph estimated MVPA mins/day.

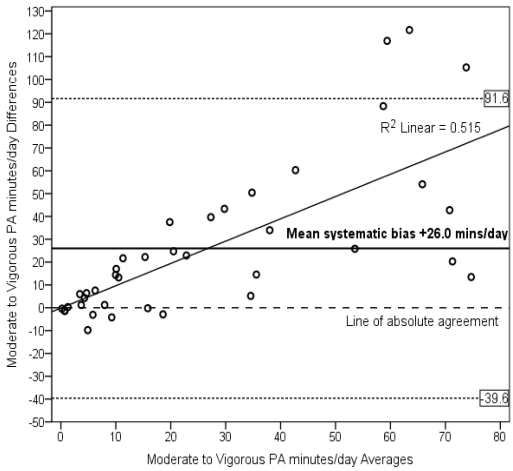


Figure 4.16 shows a moderate correlation between 7DR and Actigraph estimated MVPA (Spearman's rho = 0.55, $p < 0.001$). Associations of similar strength were observed between the two measures on dialysis days (rho = 0.53, $p < 0.001$) and non-dialysis days (rho = 0.49, $p < 0.001$) (appendices XXI a and XXI c). Bland-Altman analysis (figure 4.17) revealed that self-reported MVPA was on average 26.0 minutes (95% LOA: +91.6, -39.6) greater per day compared to objective accelerometer estimates. In addition a regression line indicates a strong positive relationship between daily MVPA averages and differences (Spearman's rho = 0.77, $p < 0.001$). As the amount of MVPA estimated increases the observed difference between MVPA values derived by each instrument becomes greater. On dialysis days observed mean bias was lower at +11.2 minutes/day (LOA: +68.1, - 45.7) and higher on non-dialysis days +37.0 minutes/day (LOA: +119.5, -45.4). For both dialysis and non-dialysis days a similar positive regression line was observed reiterating a similar divergence of outcome values with increasing MVPA volume for both conditions (appendices XXI b and XXI d).

4.3.5 Concordance of energy expenditure estimates by each instrument

Initial analysis of the relationship between EE estimated by ActivPAL (waking hour MET minutes) and Actigraph (MVPA derived kcals) revealed a moderate association (Spearman's rho = 0.52, p < 0.001). Actigraph estimated kcals were converted to MET minutes and MET minutes for accelerometer sedentary time was added to derive a comparable total daily EE value from monitor wear time. A strong correlation (figure 4.18) was observed between values from the two accelerometers (Pearson's r = 0.95, p < 0.001). The association remained similarly strong on dialysis days (Spearman's rho = 0.97, p <0.001) and non-dialysis days (Pearson's r = 0.93, p < 0.001) (appendices XXI e and XXI g).

Figure 4.18 ActivPAL versus Actigraph estimated METmins/day.

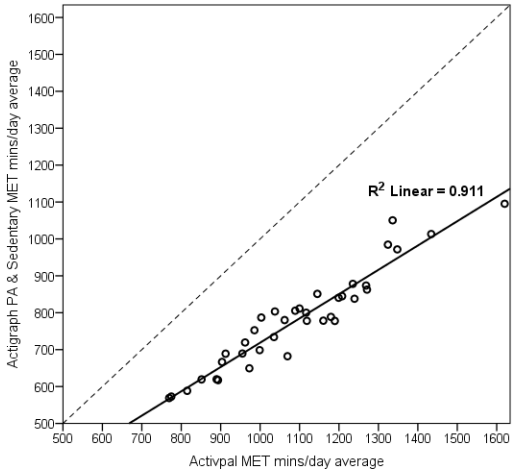
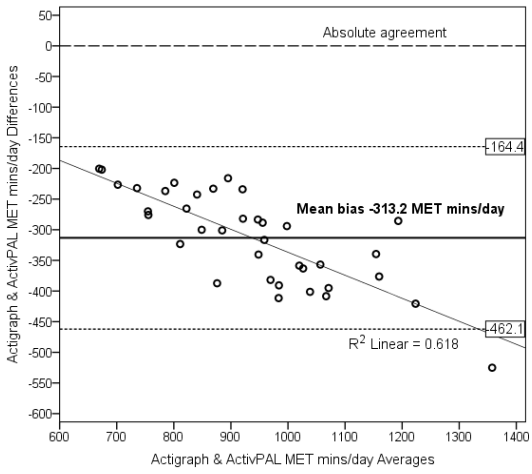


Figure 4.19 Bland-Altman plot Actigraph and ActivPAL estimated METmins/day.



Actigraph estimated EE was lower than Actigraph as determined by Bland-Altman analysis (figure 4.19) with a mean bias of -313.1 MET minutes/day (LOA: -164.4, -462.1). The mean bias and LOA were similar on dialysis days and non-dialysis days (-313 MET mins/day, LOA: -166.8, -466.5 and -310.7 MET mins/day, LOA = 143.4, -478.0 respectively. A strong correlation between the averages and differences of the measures was also found (Pearson's r = 0.79, p < 0.001) indicating greater difference in estimated EE between the accelerometers with higher EE values (appendices XXI f and XXI h).

Figure 4.20 7DR versus ActivPAL estimated METmins/day.

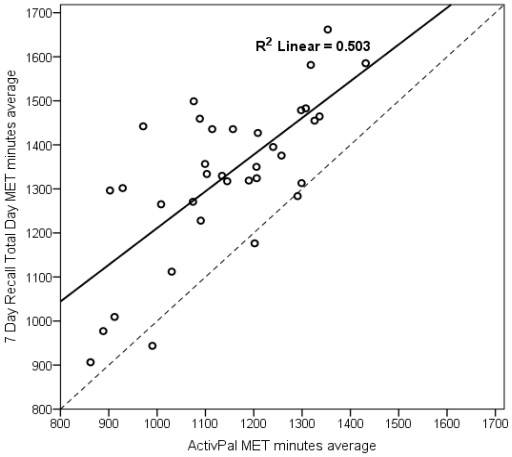
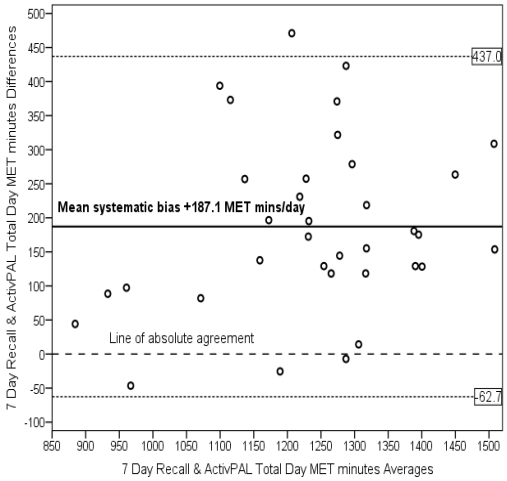


Figure 4.21 Bland-Altman plot 7DR and ActivPAL estimated METmins/day.



ActivPAL and 7DR total daily EE outcomes (figure 4.20) correlated moderately (Pearson's r = 0.71, p < 0.001), and was similarly strong on dialysis days (Spearman's rho = 0.72, p < 0.001) and non-dialysis days (Pearson's r = 0.71, p < 0.001) (appendices XXI i and XXI k and 4.7.3). Bland-Altman analysis (figure 4.21) shows comparatively higher estimation of EE by the 7DR with a mean daily bias of +187.1 MET mins/day (LOA: +437.0, -62.7 MET mins/day). Observed bias was lower on dialysis days (95.1 MET mins/day, LOA: 363.3 to -173.1 MET mins/day) and higher on non-dialysis days (256.2 MET mins/day, LOA: 549.7 to -37.3 MET mins/day) (appendices XXI j and XXII).

Figure 4.22 7DR versus Actigraph estimated kcals/day.

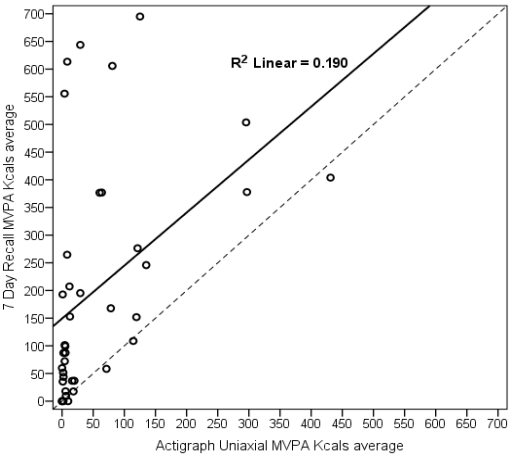
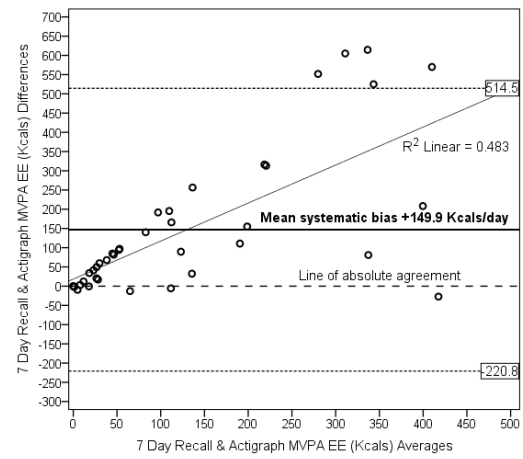


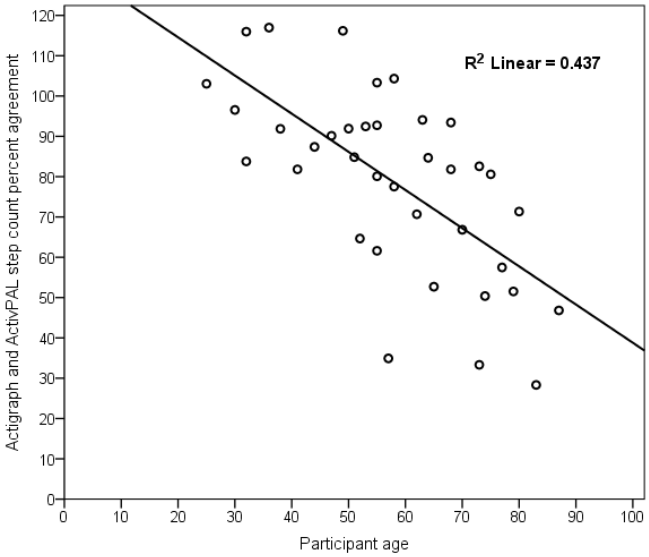
Figure 4.23 Bland-Altman plot 7DR and Actigraph estimated kcals/day.



A moderate correlation was observed between 7DR estimated MET minutes and Actigraph estimated kcals from MVPA (Spearman's rho = 0.57, p < 0.001, n = 39). The observed association was similar (figure 4.22) upon conversion of 7DR MET minutes to kcals (Spearman's rho = 0.59, p < 0.001). Non-parametric correlations remained the same for estimated EE on dialysis days (rho = 0.59, p < 0.001) and non-dialysis days (rho = 0.60, p < 0.001) (appendices XXI m and XXI o). Higher estimates of EE were derived via the 7DR compared to the Actigraph (figure 4.23) with a mean bias of 149.9 kcals/day (LOA: 514.5 to -220.8 kcals/day). Mean bias was lower on dialysis days (61.5 kcals/day, LOA: 363.2 to -240.2 kcals/day) and higher on non-dialysis days (210.9 kcals/day) with wider LOA (704.8 to -283.2 kcals). Regression analysis also showed a moderate relationship (Spearman's rho = 0.67, p < 0.001) between the averages and differences of the two methods indicating a proportional increase in measurement disparity as MVPA related EE increased. On non-dialysis days the relationship was stronger (Spearman's rho = 0.77, p < 0.001) while on dialysis days a trend was observed (rho = 0.32, p = 0.05) (appendices XXI n and XXI p).

Concordance of ActivPAL and Actigraph derived stepcounts was further explored using age, which is a recognised determinant of gait speed. A moderate inverse correlation (Pearson's r = -0.66, p < 0.001) was observed between participant age and Actigraph stepcounts as a percentage of ActivPAL estimates (figure 4.24).

Figure 4.24 Age versus Actigraph estimated stepcounts as a percentage of ActivPAL estimates.



4.4 Discussion

4.4.1 Overview of findings

A variety of subjective and objective methods have been used in previous health studies to characterise PA and sedentary behaviour of people with stage 5 CKD. This study is the first to evaluate the level of agreement between three different methods of estimating PA outcomes and sedentary behaviour. The principal findings of this study are that subjective and objective estimates of PA correlate modestly. Overall, agreement is poor with the amount of MVPA obtained via the 7DR significantly higher than estimates derived via the Actigraph and wide limits of agreement (LOA). Moderate to strong associations were found between the 7DR and objective estimates of EE. However, large significant differences in EE values and wide error limits were apparent with Bland-Altman analysis, as well as a proportional increase in measurement disparity with higher EE values. Despite strong linear associations between the Actigraph and ActivPAL estimates of sedentary behaviour and PA and low relative estimate bias, overall level of agreement was poor. Remaining PA outcomes (step counts, EE, activity counts) derived via the Actigraph and ActivPAL also demonstrated strong associations, but large significant differences and wide LOA indicated poor concordance. While adjustments may be made for estimate bias between accelerometer outcome values, these data indicate that there is considerable risk of error if ActivPAL and Actigraph outcomes are used interchangeably.

4.4.2 Relationship between Actigraph and ActivPAL step count estimates

A strong association between ActivPAL and Actigraph GT3x estimated step counts (Spearman's rho = 0.95, $p < 0.001$) in the present study compares favourably with that of Feito et al. (2012). The authors reported a correlation of $r = 0.85$ ($p < 0.001$) between these devices during two days of free living conditions in a sample of 49 normal and overweight adults. Despite the strong correlation in the current study, Actigraph recorded significantly fewer steps (mean bias -638 per day) than ActivPAL and 95% LOA were large (+576 to -1852 steps). A criterion measure was not employed in the present study to determine which monitor had the more precise estimate of step counts during seven days of 'free-living' due to feasibility issues. Findings from controlled studies using direct observation as a criterion may help to explain the large disparity in accelerometer step counts observed.

There is agreement that at moderate to brisk walking speeds, ActivPAL and Actigraph estimated stepcounts do not differ significantly from directly observed steps (Ryan et al. 2006; Sorti et al. 2008; Harrington 2011; Feito et al. 2012) or each other (Harrington et al. 2011). However, these criterion validity studies also concur that later model Actigraphs (GT1M, GT3x) show a propensity to underestimate steps taken as gait decreases below 1.0 m/s (Sorti et al. 2008; Harrington 2011; Feito et al. 2012). Although precision of the ActivPAL is also influenced by cadence slower than this threshold, an error level of 2% or less is reported (Ryan et al. 2006), however the Actigraph GT3X underestimates directly observed steps by up to 40% during slow ambulation (Sorti et al. 2008; Feito et al. 2012). It is believed that hip mounted acclerometers are especially susceptible inaccuracy at slower ambulation speeds due to reduced magnitude of vertical accelerations (Feito et al. 2011).

Importantly, age is a recognised determinant of gait speed (Bohannon 1997), and the HD population is characterised by both advanced average age and CKD mediated acceleration of ageing processes (Johansen et al. 2003b). Notably, the inverse correlation (Pearson's $r = -0.66$, $p < 0.001$) between age and Actigraph stepcounts as a percentage of ActivPAL estimates observed in this study has not been previously documented. In addition when compared to non-uraemic peers, HD patients exhibit slower self-selected and maximum gait speeds corresponding to 66% and 64% of normative values respectively (Painter et al. 2000). Slower ambulation characteristic of indoor mobility may have also contributed. ActivPAL step count accuracy is slightly lower for indoor compared to outdoor mobility (96.1% and 99.6% respectively) of healthy adults (Busse et al. 2009). Indoor PA or activities of daily living tend to be of lower intensity (Ainsworth et al. 2000) and more intermittent (Orendurf et al. 2008). Compared to treadmill protocols, cadence indoors is unlikely to be continuous, consisting instead of smaller steps to avoid obstacles (ie: sidesteps) or to maintain balance thus resulting in slower gait speed and shorter stride lengths. These factors may result in lower vertical translocation of the trunk (Actigraph) or limb (thigh) deflection (ActivPAL) and "steps" not conforming to accelerometer algorithms possibly may not identified/counted. Haemodialysis patients spend a considerable proportion of their week in a hospital. Taken together it is suggested that lower precision of the Actigraph at slower gait speeds would have a more pronounced effect on accuracy of steps taken estimated by this device in the HD population, and thus largely explains the observed disparity in the present study.

4.4.3 Actigraph and ActivPAL Sedentary and Active time estimates

ActivPAL and Actigraph estimates of sedentary behaviour correlate strongly both in minutes (Pearson's r = 0.92, p < 0.001) and as a percentage of wear time (Spearman's rho = 0.82, p < 0.001). This is in agreement with previous Actigraph/ActivPAL concordance studies reporting moderate to strong correlations for sedentary behaviour (range r = 0.68 to 0.81) during free-living situations in pre-school age children (Martin et al. 2011) and adults (Clemes et al. 2012; Matthews et al. 2013). Actigraph estimated on average 17.2 more minutes of sedentary time per day compared to ActivPAL in the present study, which is similar to the results of Matthews et al. (2013) (bias +13.2 to +19.2 mins/day) in a larger study of 216 adults. Other studies have consistently found Actigraph estimates significantly higher amounts of sedentary time compared to ActivPAL during free-living conditions (Hart et al. 2011a; Hart et al. 2011b; Clemes et al. 2012) than observed in this study (mean systematic bias range: +44 to +132 mins/day). A lower, non-significant bias of +5.2 mins/day was reported by Ridgers et al. (2012) using the Actigraph GT3X in a sample of school age children. However, the monitoring period in the latter study was comparatively short (390 minutes) as it was limited to the length of a school day, which may have reduced bias magnitude. In contrast to the present study, Martin et al. (2011) found Actigraph estimated sedentary behaviour (expressed as a percentage of wear time) for pre-school children was lower than ActivPAL (-4.3% and -2.1% corrected/uncorrected estimates). Differing findings are likely due to the authors employing a higher cutpoint (<1100 cpm) and a different interpretation of sedentary behaviour compared to the current consensus definition.

Bland-Altman analysis (figure 4.5 and 4.6) revealed relatively wide LOA of minutes and percentage of time spent sedentary around the systematic bias (90 mins and 11.4% respectively). However, this result is comparatively lower than LOA observed in previous studies employing the same cutpoint (<100 cpm), which range from 143 to 570 mins/day (Hart et al. 2011a; Hart et al. 2011b; Ridgers et al. 2012; Matthews et al. 2013) and 18.6% to 19.4% per day when normalised to monitor wear time (Martin et al. 2011). A lower sedentary behaviour cutpoint of <50 cpm suggested by Crouter et al. (2006) is reported to offer the most favourable specificity and sensitivity for detecting sitting/lying time of adults during free-living conditions (Clemes et al. 2012). However, while a lower cutpoint ameliorates mean bias between these devices, observed LOA remain wide at over two hours either side of the mean bias (Hart et al. 2011b; Clemes et al. 2012).

4.4.4 Actigraph and ActivPAL Total PA agreement

The strong correlation observed between ActivPAL and Actigraph estimates of total PA (Spearman rho = 0.84, $p < 0.001$) and no significant difference is consistent with the findings of Matthews et al. (2013) who reported similarly strong associations (rho = 0.74 and 0.79 for men and women respectively. Similarly, Matthews et al. (2013) also reported no significant difference between Actigraph and ActivPAL estimates in their larger sample of 216 adults. However, LOA in the cited study were considerably wider (-135 to 182 mins/day and -132 to 137.4 mins/day for men and women respectively) than those observed here. Conversely, Hart et al. (2011b) found that ActivPAL PA estimates were significantly lower (56.1 minutes/day) than estimates derived from an earlier Actigraph (7164) using the >100 cpm cutpoint. A higher cutpoint employed by Hart et al. (2011b) resulted a much lower non-significant difference of 11.8 minutes/day. However the definition of PA employed differed from the present study by comparing only ActivPAL estimates of 'walking' time and Actigraph ambulatory activity defined as >259 cpm.

4.4.5 Summary of ActivPAL and Actigraph outcome concordance

This is the first study to evaluate concordance of ActivPAL and Actigraph accelerometer estimates of TPA and sedentary behaviour in a clinical population. Regardless of the reason for observed discrepancies between the present study and findings in the wider literature, the unifying feature of all studies is the wide LOA reported. This is of principal concern as such high levels of random error (reflecting biological variation) between these two accelerometers at the individual level indicates their concurrent use would make accurate determination of behaviour change and stratification of risk extremely difficult. Poor agreement is probably due to the distinctive methods that each monitor employs to estimate PA and sedentary behaviour. The Actigraph uses an activity count cutpoint to differentiate these behaviours while ActivPAL employs inclinometry. Importantly, the Actigraph has been observed to record just 11 cpm for standing and washing dishes (Kozey et al. 2010), which is substantially below the <100 cpm threshold for sedentary behaviour. Consequently some routine light activities may be erroneously classified as sedentary behaviour by this device. Notably, studies employing direct observation, as a criterion measure during controlled and free living conditions, indicate that classification of sedentary behaviour by ActivPAL is more precise compared to Actigraph regardless of cutpoint applied and manipulation of monitor sensitivity (Hart

et al. 2011b; Kozey-Keadle et al. 2011; Lyden et al. 2012). Taken together it appears that regardless of cutpoint choice, size and direction of measurement bias, there is general agreement a large amount of biological variation exists between these two accelerometers and that the ActivPAL likely provides a more precise proxy measure of sedentary behaviour.

4.4.6 ActivPAL and Actigraph activity count agreement

Activity counts derived from both accelerometers for the same wear periods were very strongly associated (Spearman's rho = 0.95, $p < 0.001$). This finding is in agreement with a smiliarly strong correlation between ActivPAL and Actigraph GT3x activity counts during controlled PA (rho = 0.96, $p < 0.01$) reported by Dowd et al. (2012). Notably, these data demonstrate that although strongly correlated, a significant disparity exists between the activity counts generated by each monitor. Moreover, ActivPAL recorded proportionately more activity counts with greater amounts of PA. Such a substantive difference would appear to be unusual as the ActivPAL is a uniaxial accelerometer. The explanation for the disparity may be due to the positioning of the ActivPAL on a limb segment where greater movement and accelerations might be expected compared with the Actigraph recordings of trunk translocation. The challenge of using accelerometry to provide an objective measure of PA is in converting activity counts into outcomes that are meaningful and interpretable units (Troiano 2006). As such calibration studies for accelerometers like the Actigraph convert counts into PA intensity, step counts or EE. Although not currently part of formal ActivPAL output, activity counts from this monitor could potentially be categorised into PA intensity similar to the Actigraph. In light of the poor agreement between ActivPAL and Actigraph activity counts it is expected that cutpoints for categorising PA intensity for the former will be quite different. Dowd et al. (2012) determined the MVPA threshold for ActivPAL as >2997 cpm via indirect calorimetry in a sample of 30 adolescent females, which is considerably higher than the Freedson et al. (1998) equivalent for Actigraph uniaxial activity counts (>1952 cpm).

4.4.7 Subjective and objective estimation of light physical activity.

No relationship was observed between subjective and objective measures of light PA estimated by 7DR and Actigraph respectively. Light PA derived from the 7DR was significantly higher compared to Actigraph estimates. In contrast Leender et al. (2000) and Sirard et al. (2000) reported no significant difference between 7DR light

minutes and Actigraph (CSA 7164) derived values in samples of young adults monitored over seven days of free-living. The disparity is due to the cited study not obtaining an accelerometer value for time spent sedentary and defining all activity outside moderate to vigorous as light PA. Similarly the 7DR defines light PA as the time outside summated sleep and moderate to very hard PA for each day (Sallis et al. 1985), which thus erroneously categorises sedentary behaviour as light PA. Such an assumption ignores the fact that for the HD population a large proportion of dialysis days are spent unavoidably inactive due to the dialysis procedure itself (approximately 16 hours/week). Moreover, many individuals may experience condition related symptoms of fatigue, which is associated with further periods of sedentary behaviour (Gordon et al. 2011; Bonner et al. 2010).

4.4.8 Concordance of Actigraph and 7-day Recall MVPA

A moderate correlation (rho = 0.55, $p < 0.001$) was observed between 7DR and Actigraph GT3X estimated time in MVPA. This result sits near the middle of reported correlations (range r = 0.26 to 0.73) between the 7DR and older Actigraph (Ainsworth et al. 2000; Timperio et al. 2003; Johson-Kozlow et al. 2006) and Tri-Trac R3D (Hayden-Wade et al. 2003) accelerometers in similar sized samples of asymptomatic middle-aged to older adults. Moreover, it is strikingly similar to the corelation (r = 0.54, $p < 0.001$) reported by Garfield et al. (2011) who evaluated concordance of the 7DR with the Sensewear Armband monitor in chronic obstructive pulmonary disease patients. Overall the strength of association observed in the present study compares favourably with the average for pooled PA questionnaire and objective measure concordance studies (r = 0.37) reported by Prince et al. (2008).

A large statistically significant difference was found in the present study between 7DR and Actigraph estimated MVPA with the 7DR providing on higher average daily estimates relative compared to the Actigraph (+26 mins/day). This result is in agreement with previous studies also showing similarly large differences in daily MVPA estimates of 16.5 to 35.3 mins/day between the 7DR and accelerometry for people with severe mental illness (Soundy et al. 2007) and asymptomatic adults (Timperio et al. 2003). In contrast no significant differences were observed in larger studies comparing estimates from CSA 7164 (Actigraph forerunner) monitors and the 7DR in larger samples of middle-aged adults (Leenders et al. 2000; Johnson-Kozslow et al. 2006). The discordance in results is difficult to reconcile as all studies

including the present one employed the same MVPA cutpoint and cognitive interview technique (Sarkin et al. 1997) to recall PA. Nevertheless, as observed in the present study, all previous concordance studies reporting LOA between 7DR and accelerometer derived MVPA estimates agree that they are wide enough to exceed recommended weekly PA associated with a health enhancing effect (Timperio et al. 2003; Johnson-Kozlow et al. 2006; Soundy et al. 2007). Theoretically the systematic error observed in the present study could be corrected however, random error either side of the mean bias is more than twice daily PA recommendations (-39.6 to 91.6 minutes) indicating MVPA values from the 7DR and Actigraph may not be used interchangeably at an individual level.

Notably, the proportional relationship between the differences and averages of the 7DR and Actigraph MVPA estimates observed in the present study (Spearman's rho = 0.77, $p < 0.001$) was similar in strength to that reported by Hayden-Wade et al. (2003) ($r = 0.71$, p value not stated). Moreover visual inspection of the Bland-Altman graph of Johnson-Kozlow et al. (2006) also suggests a similar trend for overestimation with higher levels of PA, however their data were not tested for a possible relationship. Activity estimates obtained via Actigraph in the present study were summated from shorter 60-second epochs while the 7DR only records bouts of MVPA in multiples of 10 minutes. It is speculated the disparity between 7DR and Actigraph estimates would likely increase further if Actigraph estimated MVPA had been similarly been derived from valid bouts defined as ≥10 minutes. Overall, these findings agree with similar concordance studies that show poor agreement between 7DR and accelerometer estimates of MVPA thus preventing their concurrent use at an individual level (Timperio et al. 2003; Johson-Kozlow et al. 2006; Soundy et al. 2007).

4.4.9 Why are 7-day Recall and Actigraph estimates of MVPA so different?

Several factors have likely contributed to the wide disparity observed between Actigraph and 7DR estimates of MVPA in the present study. In the case of low-active participants the scoring instructions of the 7DR may be implicated in higher estimates as epochs of MVPA meeting the minimum threshold of 10 minutes are rounded up to 15 minutes. Therefore participants only just achieving 10 minutes of MVPA would have their scores inflated by up to fifty percent but this appears to have affected only three particpants. Another possible explanation is that participants may have overestimated time spent in MVPA or misclassified PA

intensity (ie: light as moderate). Measurement error associated with PA assessment is reported to increase with greater contribution of lower intensity PA to habitual activity (Durante and Ainsworth 1996). In contrast, hard or very hard PA is associated more strongly with objective measures due to being well defined and scheduled in nature and therefore easier to recall (Durante and Ainsworth 1996; Richardson et al. 2001; Timperio et al. 2003). Nonetheless, overestimation of PA greater than 4.5 METs has been documented during two days of room calorimetry monitored living (Buchowski et al. 1999). Furthermore, misclassification of PA intensity has been observed with heart rate monitoring in sedentary adults (Duncan et al. 2001).

It is also possible Actigraph may have underestimated MVPA, as hip mounted accelerometers are unable to detect increased gradient while walking (Melanson and Freedson 1995), or accurately categorise PA intensity for activities such as cycling and load bearing activities (ie: resistance exercise, carrying loads) (Westerterp 1999; Welk 2002). In addition, it is not possible to wear the Actigraph GT3x while swimming. Inspection of the 7DR records revealed that none of the included participants reported instances of swimming or resistance exercise, and just three reported cycling activity, of whom only one reported it as their main exercise activity. It would appear the disparity in estimates is thus more likely to be a combination of recognised determinants of recall accuracy (ie: age, gender, weight status, cognitive function, social desirability) (Irwin et al. 2001; Klesges et al. 2004) and relative misclassifcation of activity intensity.

The interview script for the 7DR is designed to calibrate responses by providing examples to anchor participant classification of PA. However participants may still have applied relative intensity definitions based on perceived exertion. Misclassification differences may have arisen due to broad application of the Actigraph cutpoint for MVPA, which was developed from a relatively small sample of 50 healthy, normal weight, young men and women by Freedson et al. (1998). Aerobic fitness, biomechanical efficiency, and resting metabolic rate decline as people get older (Fitzgerald et al. 1997; Byrne et al. 2005; Kozey et al. 2010), and in those who are more sedentary (Duncan et al. 2001). Consequently, an activity at a given ‘absolute intensity’ will require a greater ‘relative’ percentage of VO_{2max} with advancing age. Recent research supports the validity of the Freedson et al. (1998) cutpoints for ‘absolute’ measures of moderate and vigorous PA in 20 - 69 year olds, but not adults older than 69 (Miller et al. 2010). Furthermore, when expressed

relative to an individual's maximum aerobic fitness and age, moderate and vigorous PA intensity cutpoints were significantly different (Miller et al. 2010). Several cutpoint calibration studies employing calorimetry have suggested normalising PA intensity thresholds to co-morbidities such as diabetic and weight status (Lopes et al. 2009; Aadland and Anderssen 2012). Notably, Timperio et al. (2003) reported higher associations between self-reported and accelerometer estimated moderate PA of overweight men and women when the cutpoint was lowered from 3.0 METs ≥1952 cpm to 2.5 METs or ≥1334 cpm. Therefore, it is possible that the Freedson et al. (1998) cutpoints, may have underestimated MVPA in this sample of HD patients, a clinical population which is characterised by advanced average age and high prevalence of multi-morbidity.

4.4.10 Concordance of 7-day Recall and ActivPAL energy expenditure

Previous studies have examined concordance of 7DR and Actigraph outcomes, however this study is the first to evaluate agreement of energy expenditure (EE) estimates obtained from the 7DR, ActivPAL and Actigraph GT3x simultaneously. Moreover, it is also the first to compare ActivPAL estimates with a self-report method. While a strong correlation (Pearson's $r = 0.76$, $p < 0.001$) was observed between 7DR and ActivPAL, EE values from the 7DR were significantly higher than ActivPAL waking hour estimates (+286 MET mins/day, LOA = -9.0 to 580 MET minutes). It is difficult to determine which method may provide the more valid estimate due to the absence of a criterion EE measure. A shortcoming of the 7DR is that it assumes time outside sleep, and MVPA, is spent in light PA with no allowance for sedentary behaviour. Categorising 120 minutes of each dialysis day as resting EE was a conservative approach to enable known periods of sedentary behaviour to be correctly included. Therefore, comparatively higher EE estimation by the 7DR was inevitable, however any further attempts to manipulate EE estimation for sedentary behaviour beyond this level would have been prone to bias. While the 7DR may have overestimated EE, it is just as possible the ActivPAL underestimates EE. Only one study was located examining the criterion validity of ActivPAL EE estimation. Harrington et al. (2011) found ActivPAL significantly underestimated EE compared to indirect calorimetry at all walking speeds (from 3.2 to 7.0 km/h) during a treadmill protocol in a sample of 62 young women. ActivPAL calculates the wearer's EE from an algorithm based on step rate. However Harrington et al. (2011) argue that an equation based on ActivPAL activity counts

would be more valid given its closer association with indirect calorimetry compared to cadence ($r = 0.75$, $p < 0.001$ vs $r = 0.59$, $p < 0.001$ respectively).

4.4.11 Concordance of Actigraph and 7-day Recall energy expenditure

Actigraph and 7DR estimated EE were moderately associated in the present study (Spearman's rho = 0.59, $p < 0.001$), which is in agreement with similar 7DR concordance studies reporting moderate correlations (range $r = 0.43$ to 0.60) in samples of asymptomatic middle-aged adults (Richardson et al. 2001; Soundy et al. 2007) and people with peripheral arterial disease (McDermott et al. 2000). Leenders et al. (2000) observed a comparatively stronger correlation ($r = 0.82$ $p < 0.001$) between MVPA-based EE from the 7DR and Actigraph (CSA7164). The reason for this discrepancy may be due to their sample being very similar in characteristics to individuals recruited by Freedson et al. (1998) for development of Actigraph EE equations. Stronger associations ranging from $r = 0.76$ to 0.83 have also been reported in smaller samples of healthy adolescents (Allor and Pivarnik 2001), adults (Miller et al. 1994; Matthews and Freedson 1995) and people with COPD (Garfield et al. 2011). Comparatively stronger correlations observed in the latter studies may be due to data smoothing effect mediated by whole day EE estimates. In support of this theory Matthews and Freedson (1995) found markedly different correlations for total daily- and MVPA-based EE estimates ($r = 0.77$ and $r = 0.55$ respectively).

Overall, low agreement was observed between 7DR and Actigraph estimates of EE in the present study. The disparity between the methods was mediated largely by the divergence in EE values on non-dialysis days as no significant difference was observed between the measures on dialysis days ($Z = -1.814$, $p = 0.70$). Heterogeneity of accelerometers used in previous studies and inconsistent standardisation of EE outcome hamper direct comparison with the bias and LOA observed in the present study. However, results presented here are in agreement with several studies showing 7DR estimated EE outcomes are significantly higher than equivalent values obtained from three different accelerometers (Miller et al. 1994; Matthews and Freedson et al. 1995; Leenders et al. 2000; Allor and Pivarnik 2001). Moreover, despite observing a high correlation Leenders et al. (2000) also found Actigraph estimated significantly lower EE with a mean bias of -4.3 kcals/kg/day (LOA = -5.7, -2.6). Normalising EE values in the present study to body mass revealed a lower mean bias (-1.7 kcals/kg/day) but wider LOA (-5.9 to 2.4 kcals/kg/day). Notably, the Bland-Altman analysis of Allor and Pivarnik (2001)

revealed a proportional relationship between 7DR and Caltrac estimated EE (kcals/hr) similar to that observed in the present study. As EE increased so too did the difference between the measures.

4.4.12 Concordance of ActivPAL and Actigraph energy expenditure

Concordance of ActivPAL and Actigraph EE estimates has not been previously examined. Overall, low agreement was found between the two accelerometers for this outcome despite a strong correlation. Actigraph EE values were significantly lower than the ActivPAL and LOA were thus unsurprisingly wide. It is likely that discordance between Actigraph and ActivPAL estimated EE is mediated by several factors. Each accelerometer employs a different method to calculate this outcome. Actigraph uses an algorithm based on activity counts while the ActivPAL derives an EE estimate from step rate. Although the positioning of the devices is different, it is speculated that EE estimates from both monitors would perhaps agree more closely if the ActivPAL used an equation based on activity counts as recommended by Harrington et al. (2011). Another contributing factor may be the EE equation employed by the Actilife software, which was developed using an earlier generation of Actigraph (7164). It has been documented that this earlier Actigraph model has comparatively greater sensitivity to lower frequency movements in the light PA range, while later models such as the GT3x require comparatively greater movement to elicit a non-zero count (Rothney et al. 2008). Intuitively, lower monitor sensitivity and an attendant bias toward misclassifying light PA as sedentary would result in lower estimated EE by the Actigraph GT3X. Lastly, triaxial output from the Actigraph should in theory be more sensitive to movement than uniaxial, and may possibly provide a more valid EE estimate. The Actilife software is able to derive an EE value from triaxial activity counts. However, outcome values are a composite of EE calculated from MVPA triaxial activity counts and light PA derived from uniaxial counts using the Williams Work Energy Equation (Williams 1998). Furthermore, the Actilife software does not provide a triaxial cutpoint for sedentary behaviour, which precludes a calculation similar to that undertaken for uniaxial counts in the present study.

4.4.13 Energy expenditure concordance summary.

Controlled studies employing indirect calorimetry during walking protocols and activities of daily living indicate that existing Actigraph EE equations based on single linear regression models (Freedson et al. 1998; Swartz et al. 2000; Hendelman et

al. 2000) and two regression models (Crouter et al. 2006) underestimate EE (Welk et al. 2000; Slootmaker et al. 2009; Albinali et al. 2010). Furthermore each of the equations produce different EE values because they have been calibrated on different activities and different populations. Consequently accuracy of EE estimation using the Actigraph will likely depend on type of typical PA and population sample. Criterion validity studies of the 7DR with doubly labelled water show moderate correlations (range r = 0.47 to 0.52), with either no significant difference between the measures (Bonnefoy et al. 2001; Leenders et al. 2001) or a significant overestimation by self-report (Mahabir et al. 2006). However, wide LOA are uniformly observed with the accompanying recommendation that use of 7DR EE estimates at an individual level is limited. Leenders et al. (2001) evaluated the criterion validity of both the 7DR and Actigraph (CSA 7164) simultaneously and found estimated EE derived solely from PA by both measures correlated moderately ($r = 0.42$ to 0.55, $p < 0.05$) with doubly labelled water (DLW) measures. Although DLW and 7DR values were not significantly different, the Actigraph significantly underestimated EE by an average of 59%, however, LOA for both were equally wide. In light of poor concordance between estimates from all three instruments evaluated in the present study and documented low agreement with criterion measures there is little to recommend any one method over the other.

4.4.14 Clinical implications and further research.

Poor agreement between subjective and objective methods of estimating MVPA observed in this study and in the general literature have important implications for the use of either method to stratify risk or monitoring the effect of health interventions. The systematic bias between the measures may theoretically be corrected, however LOA are so wide that it would be difficult to stratify risk or identify change with respect to therapeutic PA recommendations. Furthermore, current consensus guidelines of 30 minutes MVPA on most days are based on findings from epidemiological studies examining associations between self-reported PA and lower CV mortality (Pate et al. 1995). Low agreement between subjective and objective measures of MVPA observed here and in the general literature suggests that PA dosage to reduce CV mortality risk using the latter will likely differ to current guidelines. Moreover there are indications that existing PA health guidelines intended for asymptomatic individuals may require re-calibration for people living with stage 5 CKD. Accelerometer studies involving Japanese HD patients demonstrate that accumulating 50 minutes or more of all intensities of PA is

independently associated with lower mortality risk (Matsuzawa et al. 2012) and maintaining the ability to ambulate (Kutsuna et al. 2010).

Importantly, the 7DR defines all free-living behaviour outside MVPA and sleep as light PA and does not differentiate it from sedentary behaviour. Hence, not only would this questionnaire erroneously classify all HD patients as meeting the 50 minutes/day of total PA threshold it is unable to quantify a behaviour metric (sedentary time) now independently associated with health outcomes. The Actigraph provides a reliable, objective, but imperfect, estimate of PA using the Freedson et al. (1998) cutpoint, which probably underestimates activity (MVPA) associated with a health enhancing effect in older adult and clinical populations with lower cardiorespiratory fitness (Duncan et al. 2001; Lopes et al. 2009; Miller et al. 2010). Further population specific calibration of Actigraph cutpoints is recommended to better utilise the triaxial output of this device in order to better characterise PA. This would assist in delineating dose response relationships between PA and health outcomes appropriate to people with stage 5 CKD.

Estimation bias for sedentary behaviour and PA values between Actigraph GT3X and ActivPAL monitors is low and could possibly be corrected using a measurement error model. However, the observed LOA are worryingly wide and more critical as they reflect a large amount of random error (just over three hours), which cannot be easily corrected with such a model. Consequently, their concurrent use to stratify risk or detect meaningful change in sedentary behaviour and total PA is not recommended. For example, the overall error margin for this outcome is more than three times wider than a threshold of ≥50 minutes/day of total PA, which is independently associated with reduced mortality risk (Matsuzawa et al. 2012) and mobility (Kutsuna et al. 2010). Moreover, using total PA values interchangeably would make detection of a clinically meaningful improvement of 10 minutes/day associated with an incremental 22% reduction in mortality risk (Matsuzawa et al. 2012) highly unlikely. Evidence suggests alternate Actigraph cutpoints such as <50 cpm (Crouter et al. 2006; Clemes et al. 2012) may ameliorate bias between ActivPAL and Actigraph sedentary estimates but they are unlikely to substantially improve random error (the inherent biological variability in physical activity behaviour) due to the fundamentally different method each device employs.

Criterion validity studies employing direct observation in controlled and free-living conditions demonstrate superior precision of the ActivPAL in classifying sedentary

behaviour and standing activities compared to Actigraph regardless of cutpoint employed and manipulation of monitor sensitivity (Hart et al. 2011b; Kozey-Keadle et al. 2011; Lyden et al. 2012). Arguably more precise estimates of these behaviours would likely result in better statistical power during analyses involving this outcome and thus indicate ActivPAL as the preferred monitor. However, studies using Actigraph monitors have identified important associations between sedentary behaviour and breaks in sedentary behaviour and health indicators (Healy et al. 2008a; Healy et al. 2008b; Gaya et al. 2009). Moreover, estimates of total PA (>1.8 METs) from waist-mounted accelerometers are predictive of mortality and mobility in the HD population (Kutsuna et al. 2010; Matsuzawa et al. 2012).

Wide LOA observed between ActivPAL and Actigraph step count estimates means direct comparison and synthesis of literature employing either device is problematic. Furthermore, concurrent use of these monitors to detect change during health interventions and stratify risk is unwise. Importantly, a PA level of <4040 steps/day among HD patients is associated with levels of serum high density lipoprotein (<1.03 mmol/L) predictive of increased CVD risk (Masuda et al. 2009). Although an individual might record 3500 steps with the Actigraph the ActivPAL value may be anywhere between 5352 and 2924. In addition, an increase of 1000 steps/day is independently associated with meaningful reductions blood pressure in type 2 diabetes (Manjoo et al. 2010) and 10% lower risk of metabolic syndrome (Sisson et al. 2010). Although minimum detectable change for the ActivPAL is 45 steps (Dahlgren et al. 2010), an additional 2428 steps would have to be performed in order to detect a meaningful increase if these devices were used concurrently.

Criterion validity studies indicate ActivPAL step count estimates have the highest precision of available ‘field’ methods (Grant et al. 2006; Ryan et al. 2006; Harrington et al. 2011; Feito et al. 2012). Furthermore, in light of the finding that ActivPAL and Actigraph GT3X step count agreement declines with advancing age, use of the latter device to monitor step counts of people with stage 5 CKD is not indicated. This recommendation is made with the caveat that an earlier version of the Actigraph (CSA7164) is reported to have superior step count validity (Le Masurier et al. 2004; Kozey et al. 2010; Feito et al. 2012). Similar step count accuracy may possibly be achieved with the GT3X by applying the low frequency filter extension and is suggested as an area worthy of further exploration.

One advantage of the Actigraph accelerometers is their extensive use in health studies to categorise PA intensity using activity count cutpoints. A potential advantage of cutpoints calibrated for the ActivPAL is the adoption of one monitor that can categorise PA intensity in addition to having superior accuracy in estimating sedentary behaviour, step counts and transitions compared to the Actigraph GT3X. These data indicate currently available uniaxial cutpoints may not be applied to the ActivPAL activity count output. To optimise utility of output from this device population specific calibration that allows ActivPAL activity counts to be categorised into different levels intensity should be undertaken. This might also facilitate easier comparison of PA derived EE estimates with other accelerometers.

Poor levels of agreement were observed between 7DR, ActivPAL and Actigraph estimates of EE in the present study. There is general agreement in the literature that current EE prediction equations for ActivPAL and Actigraph underestimate EE compared to 'gold standard' measures (Leenders et al. 2001; Albinali et al. 2010; Harrington et al. 2011) while the 7DR provides higher estimates, and demonstrates a similar lack of precision (Bonnefoy et al. 2001; Leenders et al. 2001; Mahabir et al. 2006). Low criterion validity is likely mediated by these instruments not taking into account participant characteristics (ie: age, gender, adiposity, efficiency of movement, environmental and geographic conditions), which explain 64% of the observed variation in total EE in healthy individuals (Plasqui et al. 2005). Inherent limitations of questionnaire-based EE estimates calculated from the Compendium of Physical Activities have been highlighted by Kozey et al. (2010). Consequently the true EE for someone with stage 5 CKD may not be accurately determined by either accelerometers or self-report. Therefore neither method can presently be recommended over the other to provide a proxy measure of individual EE during free-living conditions. Accelerometer and self-report estimates of EE may have a useful role in comparing standardised estimates to rank individuals but they may not be used interchangeably in the stage 5 CKD population.

4.4.15 Study limitations

The sample included for final analysis in the present study was of moderate size but similar to previous studies evaluating the concurrent validity of ActivPAL and Actigraph. While participants' demographic and clinical characteristics are similar to those reported for the Scottish HD population (SRRR 2013), caution is advised when generalising these findings given the degree of gender bias (72 - 80% male

depending on outcome). This may have resulted in higher associations between subjective and objective estimates of MVPA, as self-report accuracy is reportedly lower for women (Richardson et al. 2001; Timperio et al. 2003). However, gender differences in PA recall accuracy reported in the literature are largely attributed to greater male participation in vigorous activities which are more easily recalled (Durante and Ainsworth 1996; Richardson et al. 2001), which was not a feature apparent in this study. In addition, gender did not influence correlations between objective and subjective MVPA estimates during exploratory post-hoc analysis.

Waist and lower limb mounted accelerometers will likely miss aspects of PA that involve upper body movement and may lack sensitivity in detecting additional EE attached to load carrying or walking on an incline. However, walking is the most prevalent form of PA during free-living (Troiano et al. 2008) and was the most commonly reported activity in this sample of HD patients. Furthermore, improvements in PA measurement precision with simultaneous upper limb monitoring are slight and offset by the burden of cost and additional data processing of an extra accelerometer (Swartz et al. 2000). Due to time constraints and a desire to minimise participant burden measures of individuals' resting metabolic rate were not employed to assist with EE estimates. Lastly, these findings are presented with the caveat that this is a concordance not a criterion validity study. None of the PA assessment methods evaluated here are recognised as 'gold standard'. Recommendations regarding instrument selection for monitoring sedentary time and PA behaviour in stage 5 CKD are thus based on the weight of findings from the present study and the general literature, and summarised in table 4.5.

Table 4.5 Assessment methods recommended for behavioural outcomes.

	ActivPAL	Actigraph	7DR
Sedentary time	**+++**	++	NA
Light PA	NA	+	-
Mod-vig PA	NA	+	+
All PA (all postures)	++	**+++**	-
PA (standing only)	**+++**	++	-
Steps taken	**+++**	++	NA
Energy Expenditure	+	+	+

Key: NA not applicable, - not recommended, + cautiously recommended, ++ moderately recommended, +++ highly recommended

4.5 Conclusion

Overall findings from the present study underline the point that while correlational analysis indicates the strength of the linear relationship between two outcomes it does not accurately reflect their level of agreement. Actigraph and 7DR estimates of PA may not be used interchangeably nor may PA data of HD patients obtained via subjective and objective methods be pooled presently. Accelerometry is the preferred method for PA surveillance given its superior ability to differentiate light and sedentary behaviour. Accelerometer choice will depend on the outcome of interest. Actigraph and ActivPAL may not be used concurrently to estimate sedentary behaviour and step counts, and on balance ActivPAL likely provides more valid estimates of these outcomes. However, this may not preclude the use of Actigraph GT3X to estimate PA and sedentary behaviour. If the desired outcome is PA associated with a health enhancing effect then the Actigraph GT3X is recommended with the proviso that cutpoints are appropriately calibrated to the target population. Actigraph output should otherwise be reported as activity counts per minute only. Energy expenditure estimates from all three methods should not be used interchangeably, but may still have a useful role at an epidemiological level.

What is known about this topic:

- Physical activity and sedentary lifestyles are implicated in life expectancies of HD patients.
- There is little uniformity of methods used to assess PA in the stage 5 CKD population.
- Information regarding concordance of assessment instruments to estimate PA outcomes and sedentary behaviour of people with stage 5 CKD is scant.

What this study adds:

- Subjective and objective estimates of PA investigated in the present study may not be used interchangeably in the CKD 5 population.
- ActivPAL is likely a more precise instrument for estimating sedentary time and step counts in the HD population.
- The Freedson et al. (1998) cutpoints for categorising Actigraph activity counts may be inappropriate for the HD population.
- Actigraph output should be reported as counts per minute
- Actigraph, ActivPAL and 7DR may not be used interchangeably for estimates of EE.

Chapter 5: Correlates of physical function in stage 5 CKD

5.1 Introduction

5.1.1 Severity and prevalence of impaired physical function

Stage 5 chronic kidney disease (CKD) is characterised by severely reduced physical function compared to non-uraemic peers across all three levels of the International Classification of Functioning, Disability and Health (ICF) model (body functions and structures, activity, participation) (WHO 2001). At a physiological level cardiorespiratory fitness (CRF) of HD partients is on average 60 - 70% of predicted VO_{2peak} values (Cheema and Singh 2005; Johansen 2007; Parsons and King-Van Vlack 2009; Segura-Orti 2010; Smart and Steele 2011). In addition, indices of directly measured lower limb neuromuscular function are 22% to 45% lower than age-matched controls (Johansen et al. 2003a; Blake and O'Meara 2004).

Measures of functional capacity obtained via physical performance-based tests of CRF are reported to be 61% lower than norm values (Greenwood et al. 2012), while composite measures of neuromuscular function and mobility such as the timed up-and-go (TUAG) and self-selected gait speed reflect values for adults of more advanced age (Bohannon et al. 1995; Painter et al. 2000; Johansen et al. 2001a; Jamal et al. 2006; Greenwood et al. 2012). Moreover, proxy measures of endurance and lower limb power demonstrate more profound impairment among older maintenance HD patients (Painter et al. 2000).

At a participation level, patient-reported outcomes of self-reported functional status are consistently well below norm values (DeOreo 1997; Painter et al. 2000; Tawney et al. 2000; Mapes et al. 2003). This is underlined by findings from the Comprehensive Dialysis Study showing functional status of almost all 1547 participants at or below the 50^{th} percentile for controls aged >70 years (Johansen et al. 2010b). Furthermore, prevalence of disability with one or more basic activities of daily living (ADL) among maintenance HD patients is significantly higher than community dwelling older adults (McAdams-Demarco et al. 2012).

5.1.2 Predictive utility of physical function outcomes

Reduced physical function across the spectrum of the ICF has profound implications for quality of life and prediction of health outcomes in the HD population (De Oreo 1997; Stenvinkel et al. 2002; Mapes et al. 2003; Sietsema et al. 2004; Stack et al. 2005; Jamal et al. 2006; McAdams-Demarco et al. 2012). A CRF level above a

threshold of 17.5 ml/kg/min is independently associated with significantly lower mortality among prevalent HD patients (Sietsema et al. 2004) and at all stages of the CKD trajectory (Gulati et al. 2012). Neuromuscular function tests from isolated muscle group contraction to composite measures of lower extremity power, balance and mobility assessments are similarly predictive. Low isometric grip strength assessed at the initiation of HD is independently associated with higher mortality among male patients (Stenvinkel et al. 2002). Poor TUAG performance (>10 seconds) among elderly HD patients is associated with bone fractures (Jamal et al. 2006) and an almost seven fold risk of dependency with one or more basic ADLs (Cook and Jassal 2008). Worryingly, slow sit-to-stand test times and high prevalence (65%) of slow gait (<1.0 m/s) in the HD population (Painter et al. 2000) are associated with higher risk of mortality, falls, hospitalisation and dependent living in older adults (Buatois et al. 2008; Tiedeman et al. 2008; Braden 2012).

Large-scale studies also attest to the predictive utility of patient-reported functional status. Low physical component summary (PCS) scores (<25) from the SF-36 questionnaire are associated with a 93% higher risk of death and 56% higher risk of hospitalisation (Mapes et al. 2003). Notably, a 10 point decrease in PCS score is associated a 25% increased risk of death within one year (Knight et al. 2003; Mapes et al. 2003), while five point increases are associated with incremental reductions in adjusted risk of 10% (DeOreo et al. 1997; Lowrie et al. 2003; Mapes et al. 2003). Worryingly, mortality risk among HD patients is more than threefold higher for individuals with one or more ADL disability compared to those without disability (McAdams-Demarco et al. 2012). Importantly, physical function remains predictive of hospital admissions, graft survival and mortality even after kidney transplant (Houle et al. 2002; Kutner et al. 2006; Yango et al. 2006).

5.1.3 Justification for exploring correlates of physical function in CKD 5

It appears that commencement of HD therapy precipitates a decline in physical function towards frailty and dependency (Johansen et al. 2010a), which persists to some degree even after uraemia has been reversed by kidney transplant (Greenwood et al. 2012). Identifying risk factors of poor physical function to accurately target health interventions for this condition should therefore be a priority. While physical function declines with age and comorbidity, people with stage 5 CKD experience a more profound decline and there are indications that this may be mediated by uraemia *per se*. Difficulty in performing one chair rise and declining

self-reported functional status is significantly associated with increasing renal impairment (Chow et al. 2003; Kurella et al. 2004; Brodin et al. 2008). Furthermore, histological studies report evidence of uraemic myopathy induced via mechanisms of inflammation and protein catabolism (Ahonen et al. 1980; Brautbar et al. 1983; Diesel et al. 1990; Diesel et al. 1993), while HD dosage is also associated with physical function (Johansen et al. 2001a).

Low physical activity (PA) is also believed to be a contributor to muscle wasting and impaired physical function via a potent triad of enforced inactivity (during HD therapy), fatigue (associated with uraemia and the HD procedure), and worsening comorbidity (UKRR 2012). Worryingly, only 13% of HD patients achieve recommended PA levels (Painter et al. 2011) and they are on average 35% less active than sedentary non-uraemic peers (Johansen et al. 2001b). Recent PA is the most important modifiable determinant of CRF (Bouchard and Perusse 1994) and several reviews concur that structured PA programmes improve physical function in stage 5 CKD (Parsons and King-van Vlack 2009; Segura-Orti 2010; Smart and Steele 2011). However, studies investigating the influence of habitual PA on contemporaneously assessed physical function in stage 5 CKD are either small in scale (Johansen et al. 2001a), or limited to just one outcome (Kutsuna et al. 2010).

5.1.4 Summary

Reduced physical function is highly prevalent amongst and implicated in the health outcomes of people with stage 5 CKD, facts that remain unchanged even after reversal of uraemia by kidney transplantation. Exploration of the determinants of physical function from routinely monitored clinical variables, and the specific contribution of PA, therefore appears warranted. Such observations may help inform recommendations regarding use of physical function outcome monitoring (and possibly interventions) to help ameliorate the decline towards frailty that many people receiving HD therapy for stage 5 CKD experience.

The objectives of this study were to:

- Explore the correlates of objective measures of physical function (physical performance) of people with stage 5 CKD.
- Explore the correlates of subjective measures of physical function (self reported functional status) of people with stage 5 CKD.
- Explore the influence of objectively estimated physical activity on objectively and subjectively determined physical function of people with stage 5 CKD.

5.2 Methods

5.2.1 Study design, participant recruitment and inclusion/exclusion criteria

This cross-sectional study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the West of Scotland Research Ethics Committee and the Monklands Hospital Research and Development Department. This was a prospective cohort study involving 80 self-selected volunteer participants, aged >18 years, ambulant with or without a walking aid, and undergoing maintenance HD therapy for stage 5 CKD. Participants were recruited from an NHS outpatient HD unit at Monklands Hospital, Airdrie. Participants were screened by their physician to verify their eligibility for the study. The following exclusion criteria were applied: pregnancy, unstable cardiovascular conditions, recent cerebrovascular event, recent pulmonary thromboembolism, excessive inter-dialytic weight gain determined by physician, use of corticosteroids and anabolic therapies, recent pulmonary embolism, serum potassium >6 mmol/L, infection or course of antibiotics within one month of study period. Individuals were ineligible if they had diagnosed with dementia/severe cognitive impairment, or were not fluent in written and spoken English. Written informed consent was obtained from each participant prior to study commencement.

5.2.2 Demographic and clinical measures

Anthropometric and clinical measures (age, height, weight, BMI, resting heart rate, resting blood pressure) were taken prior to assessment of physical performance (general methods 2.1.3). The following biochemistry measures were obtained from review of recent pre-dialysis blood tests (general methods 2.6.1): dialysis adequacy (urea reduction ration), haemoglobin, haematocrit, C-reactive protein, albumin, serum phosphate, corrected serum calcium, parathyroid, pre-dialysis creatinine. Other measures included a simple additive score of comorbidity, which was obtained from review of participants' electronic hospital records.

5.2.3 Assessment of physical function

Physical function data for this study were collected between November 2011 and August 2013 and assessments were administered to participants during one session on an inter-dialytic day. Functional capacity was measured using physical performance measures of grip strength, lower limb power, functional mobility and cardiorespiratory fitness (CRF). These tasks were chosen as they are necessary for

performance of ADLs and are predictive of health outcomes for people with stage 5 CKD and older adults. Grip strength of the dominant upper limb was obtained with a JAMAR dynamometer (Sammons Preston, Inc., Bolingbrook, IL) in a standardised sitting position with the best of three attempts recorded (general methods 2.3.1). A proxy measure of lower limb power was obtained using the sit-to-stand 5 test (STS5). Participants completed five sit-to-stand movements as quickly as possible without upper limb assistance from a chair height standardised to their stature (general methods 2.3.2). The timed up-and-go test provided a composite measure of lower limb power, balance and functional mobility. Participants stood up from a standard height chair, walked three metres, turned once they had drawn level with a marker cone, returned and sat down (general methods 2.3.3). Participants were allowed the use of a walking aid as required. The fastest performance of two attempts at the STS5 and TUAG were recorded to the nearest tenth of a second. A proxy measure of CRF was obtained via a symptom limited incremental shuttle walk test (ISWT) as per general methods section 2.3.4. Participants' heart rate response was monitored (general methods 2.3.4.1) throughout, and the test was terminated according to ACSM (2010) guidelines for exercise testing (general methods 2.3.4.4). Distance walked, final gait speed and a CRF level in metabolic equivalents (METs) derived from gait speed at test termination were recorded (general methods 2.3.4.5). Measures of self-reported functional status were obtained via the Duke activity status index (DASI) (general methods 2.4.1) and from the summary physical component summary (PCS) score of the Kidney Disease Quality of Life - Short Form™ (KDQOL-SF) UK English version 1.2 (Hays 1994). The reader is referred to the general methods section for further information on questionnaire scoring.

5.2.4 Measurement of physical activity

Estimates of PA were obtained via triaxial accelerometry using the Actigraph GT3X (Actigraph Corp, Pensacola, Florida). Participants kept a wear log (appendix V b) and also wore an ActivPAL (PAL Technologies Ltd, Glasgow) monitor to accurately determine their Actigraph monitor wear time. Both monitors were synchronised and worn as per general methods sections 2.5.2 and 2.5.7 on their non-dominant side. Accelerometers were retrieved from participants on day nine, which coincided with a routine HD appointment and data were downloaded using the proprietary Actilife and ActivPAL software. Actigraph PA data were reduced as per general methods sections 2.5.4 and 2.5.8 and only participants with a minimum of eight hours monitor

wear on one dialysis day and two non-dialysis days were included for final analyses (as per recommendations of chapter 3).

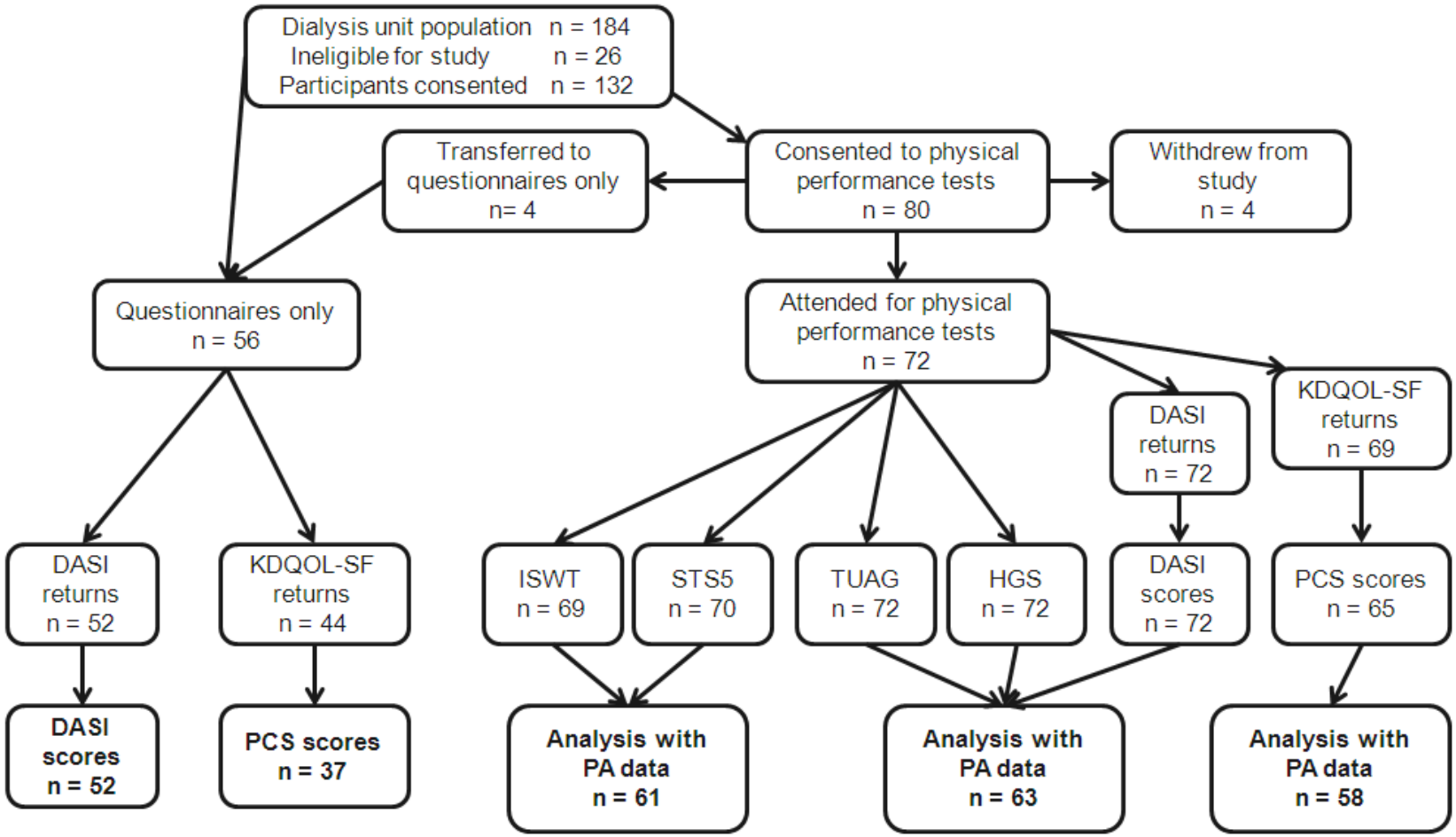
5.2.5 Data analysis

Data analysis was undertaken using the Statistical Package for Social Science (SPSS, Illinois, USA), version 19.0. Sample characteristics are presented as mean and standard deviation (SD) or median and interquartile range according to being determined as parametric or non-parametric respectively by the results of Kolmogorov-Smirnov normality tests. Differences between groups for the same variable were tested using an independent t-test or Mann-Whitney U test for normal and non-normal data respectively. Associations between physical function measures and demographic and clinical variables were undertaken using Pearson product-moment correlation analysis. Variables associated with physical function outcomes, which had a correlation of >0.20 and a significance level of ≤0.05 were identified as candidate predictor variables. If the minimum ratio of variables to sample size for multiple regression analysis recommended by Harris (1985) was violated a selection process was employed to reduce the number of variables. Variables were not selected for entry to the multiple regression analysis if their β coefficient and confidence intervals approached zero. If variables exhibited collinearity, partial correlation analysis was used to select the most robust variable for model entry. Backward stepwise regression analysis was used with the selected candidate variables. Physical activity was subsequently added to the model containing only the retained clinical and demographic variables to explore the possible contribution of this behaviour variable to the outcome. If PA was also retained in the model, the amount of outcome variance explained by this behaviour variable was reported. Statistical significance for multiple regression analysis was set at a two-tailed value of $p < 0.05$. The correlation between the dependent and independent variables are reported as well as the amount of variance explained. Adjusted r^2 values are also reported, as the standard r^2 value tends to inflate as a function of the number of predictor variables retained in the model (Altman 1995). The relative importance of variables retained in the prediction models was subsequently determined by separately entering each variable into the model to partition the variance explained. Residual analysis for each of the multiple regression analyses was also undertaken to check for outliers and that the assumptions for multiple linear regression analysis were not violated.

5.3 Results

Figure 5.1 shows the process by which participants' data was included for analysis. A total of 132 people registered interest in the study, of who 80 agreed to take part in physical performance testing. Four people did not attend their appointment and withdrew their consent, while four later declined the physical performance tests but agreed to complete the questionnaires. In total 56 people consented to complete only the questionnaire part of the study, and 72 people participated in the physical performance tests and questionnaire sections of the study. Return rate for the Duke and KDQOL-SF forms was lower in the questionnaire only group (93% and 80% respectively) compared to the exercise test group (100% and 96% respectively). Of the 72 participants who took part in the physical tests two people were unable to perform the STS5 test, and three people declined the shuttle walk test. Two participants declined or were unable to wear the Actigraph and another seven participants lacked sufficient accelerometer wear time for final analyses. A score for the DASI was successfully obtained for all participants in both groups. However, successful completion rate for the PCS was lower due to missed responses in the KDQOL-SF. Summary PCS scores were obtained for 65 of the 72 (90%) people who attended the physical performance tests, and 37 out 44 (84%) of the questionnaire only group.

Figure 5.1 Flowchart of patient participation and inclusion for multiple regression analyses.



5.3.1 Sample characteristics

Demographic and clinical characteristics for participants with minimum required monitor wear time are reported in table 5.1 and are not significantly different to the initially recruited sample of 72 participants (appendix XXII a). Participant age ranged from 24 to 87 years, with 35 percent of the sample aged 65 years or older. Women made up 37 percent of the sample, and were significantly younger ($t(61) = 2.93$, $p = 0.005$) than men (50.5 ± 13.6 versus 61.6 ± 15.1 respectively). Diabetics accounted for 25 percent of the sample.

Table 5.1 Demographic and clinical characteristics participants with sufficient PA data for final analyses. Data are presented as mean ± SD, or median (IQR) for normal and non-normally distributed data respectively.

Characteristic	Performance tests	Questionnaires only
Age *(years)*	57.5 ± 15.5	62.8 ± 16.9
Gender *M/F (%)*	40 / 23 (63/37)	24/27 (47/53)
Body Mass Index *(kg/m^2)*	28.7 ± 6.3	
Resting Heart rate *(bpm)*	71.7 ± 12.4	
Systolic *(mmHg)*	134.7 ± 23.8	
Diastolic *(mmHg)*	75.5 ± 9.8	
Systemic pulse pressure *(mmHg)*	53 (43 - 70)	
Mean arterial pressure *(mmHg)*	95.2 ± 11.9	
Haemodialysis Vintage *(months)*	14.8 (6.8 - 31.4)	14.7 (6.3 - 37.0)
Renal Replacement Therapy Vintage *(months)*	25.9 (8.3 - 69.3)	20.2 (6.8 - 40.3)
Haemoglobin *(g/dL)*	11.2 ± 1.0	11.0 ± 1.3
Haematocrit *(%)*	33.9 ± 3.2	33.6 ± 3.9
C-reactive protein *(mg/L)*	0 (0 - 10.0)	8.0 (0 - 13.0)
Dialysis Adequacy *(%)*	71 (66 - 75)	72 (67 - 77)
Albumin *(g/L)*	39.0 (36.0 - 41.0)	37.0 (35.0 - 39.0)
Troponin T *(ng/L)*	37.0 (21.0 - 69.0)	54.0 (31 - 104)
Corrected Calcium serum level *(mmol/L)*	2.37 ± 0.17	2.37 ± 0.16
Phosphate *(mmol/L)*	1.40 ± 0.33	1.60 ± 0.84
Parathyroid level *(mmol/L)*	16.4 (9.7 - 30.9)	16.7 (8.1 - 29.1)
Creatinine pre-dialysis *(µmol/L)*	644 (546 - 856)	
Total number of medications	10 (8 - 12)	
Number of comorbidities, *(N)*	1.0 ± 0.8	
• Hypertension *(%)*	35 (56)	
• Diabetes mellitus *(%)*	16 (24)	
• Cardiovascular disease *(%)*	13 (21)	
Duke activity status index	22.2 (15.5, 34.2)	17.8 (7.2, 25.0)
KDQOL-SF Physical component score	32.9 (9.1)	31.4 (10.0)
KDQOL-SF vitality	36.5 9 (23.1)	38.7 (23.6)
Leicester Uraemic Symptom Scale	36.3 (17.3)	32.1 (17.8)

In contrast women made up more than half of the questionnaire only group, while independent t-test revealed participants in this group were significantly older than those who undertook physical performance testing ($t(122) = -2.42$, $p = 0.02$). Mann-

Whitney U test indicated troponin T and C-reactive protein levels were significantly higher in the questionnaire only group (U = 1326, p = 0.007 and U = 960, p < 0.001 respectively) but there were no differences observed between the groups in terms of other biochemistry indices or dialysis vintage. Significantly lower DASI scores were observed for the questionnaire only group (U = 1191, p = 0.001) while KDQOL-SF physical component scores (PCS), self-reported vitality and symptom burden (LUSS) were not significantly different.

Sample characteristics for physical function and PA are presented in table 5.2. Men recorded significantly higher hand grip strength, Duke activity status index, and PCS (t(61) = 6.62, p < 0.001, U = 298, p = 0.02 and U = 242, p = 0.03 respectively) compared to women. A large effect size was observed for HGS while medium effect sizes were seen for the DASI and PCS (appendix XXII b). Women were significantly more active than men (U = 306, p = 0.03) with a small to medium effect size observed (appendix XXII b) and were on average 8.7 years younger (t(71) = 2.33, p = 0.02). Mann Whitney U-test revealed that DASI scores for the questionnaire only group (median = 13.5, IQR = 7.2 - 25) were significantly lower than those performing the physical tests (U = 1237, p = 0.001). Although PCS scores for the questionnaire only group were generally lower (median = 29.5, IQR = 23.0 - 37.0) the difference was not statistically significant (U = 1177, p = 0.54).

Table 5.2 Participant physical performance, self-reported physical function, and physical activity characteristics. Data are presented as mean ± SD, or median (IQR) for normal and non-normally distributed data respectively.

Outcome	Men & Women	Men	Women
Grip strength *(Kg)*	30.9 ± 10.1 †	35.8 ± 8.1	22.35 ± 7.1
Sit to Stand 5 test *(seconds)*	11.7 (9.5, 15.5) ††	11.8 (9.5, 14.6)	11.14 (9.3, 16.4)
Timed Up and Go test *(s)*	7.62 (6.28, 10.8) †	8.08 (6.23, 10.8)	7.03 (6.3,13.3)
Shuttle walk test distance *(m)*	280 (150, 430) ††	260 (140, 440)	335 (168,408)
Duke Activity Status Index	22.2 (15.5, 34.2) †	27.0 (16.9, 36.7)	18.7 (10.7, 30.2)
KDQOL-SF PCS	30.6 (24.7, 38.7) †††	32.9 (27.4, 40.6)	27.8 (22.8, 32.4)
Physical activity (Triaxial cpm)	289 (183 - 397) †	245 (147, 387)	322 (259, 450)

† n = 63, †† n = 61, ††† n = 58.

5.3.2 Univariable associations with physical performance

The number of clinical and demographic variables significantly associated with the range of physical performance attributes increased with greater complexity and physiological demand of the task (table 5.3).

Table 5.3 Univariable associations of demographic and clinical measures with physical performance outcomes.

	Grip strength (n = 63)		Sit-to-stand 5 (n = 61)		Timed up-and-go (n = 63)		Shuttle walk test (n = 61)	
Variable	Unstandardized β (Lower, Upper Bound)	r	Unstandardized β (Lower, Upper Bound)	r	Unstandardized β (Lower, Upper Bound)	r	Unstandardized β (Lower, Upper Bound)	r
Weight	0.21** (0.06, 0.36)	0.34**	Not associated		Not associated		Not associated	
Height	0.24** (0.10, 0.38)	0.40**	Not associated		Not associated		Not associated	
Gender	-13.5***(-17.5, -9.4)	-0.65***	Not associated		Not associated		Not associated	
Age	Not associated		0.16**(0.07, 0.26)	0.40**	0.16***(0.09, 0.24)	0.48***	-6.92***(-9.97, -3.87)	-0.51***
Medications	-0.9*(-1.65, -0.14)	-0.29*	0.70**(0.22, 1.19)	0.36**	0.34 (-0.06, 0.74)	0.21*	-23.09**(-38.81,-7.37)	-0.36**
Creatinine	0.02**(0.01, 3.16)	0.36**	Not associated		-0.01*(-0.012, -0.001)	-0.29*	0.38**(0.10, 0.66)	0.34**
Albumin	0.73*(0.12, 1.34)	0.29*	Not associated		-0.64***(-0.93, -0.36)	-0.50***	17.47**(4.5, 30.43)	0.33**
CRP			0.20**(0.06, 0.34)	0.34**	0.20**(0.08, 0.31)	0.41**	-6.62*(-12.03, -1.2)	-0.30*
Comorbidities					1.88*(0.27, 3.49)	0.29*	-75.17*(-140.85, -9.5)	-0.29*
Diastolic Bp					-0.16*(-0.29, -0.03)	-0.30*	Not associated	
Troponin-T					0.04***(0.03, 0.06)	0.54***	-1.08**(-1.83, -0.33)	-0.35**
Phosphate					-4.77* (-8.64, -0.9)	-0.30*	223.0**(67.0, 379.0)	0.35**
BMI							-9.21*(-17.64, -0.79)	-0.27*
Pulse pressure							-3.08*(-5.39, -0.77)	-0.33*

* p < 0.05, ** p < 0.01, ***p < 0.001

5.3.3 Univariable associations with self reported functional status

Table 5.4 reports the results of correlation analyses between clinical and demographic variables, and scores derived from functional status questionnaires investigated in this study.

Table 5.4 Univariable associations with self-reported functional status.

	Duke Activity Status (n = 63)		KDQOL PCS (n = 58)	
Variable	Unstandardized β (Lower, Upper bound)	r	Unstandardized β (Lower, Upper bound)	r
Comorbidities	-5.47* (-9.85, -1.09)	0.30*	-3.13* (-6.15, -0.12)	-0.27*
Creatinine	0.02* (0.002, 0.041)	0.28*	0.035 (0.007, 0.063)	0.32*
Gender	-7.38* (-14.65, -0.11)	-0.25*	-5.65* (-10.74, -0.56)	-0.29*
Medications	-1.81** (-2.82, -0.8)	-0.42**	Not associated	
CRP	-0.16* (-0.30, -0.02)	-0.28*	Not associated	
Parathyroid	0.17* (0.002, 0.337)	-0.25*	Not associated	
Albumin	Not associated		0.77* (0.18, 1.35)	0.33*

*p < 0.05, **p < 0.01, ***p < 0.001. CRP = C-reactive protein

5.3.4 Associations between physical function status and physical activity

All measures of physical function and functional status were associated with PA except hand-grip strength (HGS). Moderate correlations were observed for PA and physical performance while more modest associations were seen with self reported physical function (table 5.5).

Table 5.5 Associations between physical activity, physical performance and functional status outcomes.

Function outcome	Unstandardized β (Lower bound, Upper bound)	r
Hand grip strength (kg)	0.001 (-0.01, 0.012)	0.12, p = 0.95
Sit-to-stand 5 (s)	-0.012 (-0.018, -0.005)	-0.42***
Timed up-and-go (s)	-0.010 (-0.015, -0.005)	-0.46***
Shuttle walk distance (m)	0.626 (0.457, 0.795)	0.69***
Duke activity status index	0.016 (0.001, 0.031)	0.26*
KDQOL-SF PCS	0.013 (0.003, 0.022)	0.32**

* p < 0.05, ** p < 0.01, ***p < 0.001, n = 63

5.3.5 Hand-grip strength multiple regression analysis

The following five variables associated with grip strength were retained and entered for multiple regression analysis: gender; number of medications; creatinine; albumin; weight; height. The subsequent model, which retained gender and albumin as predictor variables explained almost half of the variance in hand-grip strength (table 5.6). Physical activity was not retained as a predictor when added to this model

Table 5.6 Hand-grip strength multivariable regression models without and with physical activity as an additional predictor.

Variable	Unstandardized β (Lower, Upper bound)	Unstandardized β (Lower, Upper bound)	r^2 contribution
Gender	-13.50*** (-17.48, -9.42)	-13.08*** (-16.97, -9.2)	0.39***
Albumin	0.60* (0.06, 1.13)	0.62* (0.15, 1.09)	0.06*
Physical Activity	Not added	0.005 (-0.003, 0.014)	p = 0.22
r	0.70	0.69	
r^2	0.49	0.48	
r^2 adjusted	0.47	0.46	

* p < 0.05, ** p < 0.01, ***p < 0.001 (n = 63)

5.3.6 Sit-to-stand 5 multivariable regression analysis

Variables entered for multiple regression analysis for STS5 performance were: age; number of medications; C-reactive protein; comorbidity score.

Table 5.7 Results of sit-to-stand 5 multivariable regression analysis without and with physical activity as an additional predictor.

Variable	Unstandardized β (Lower, Upper)	r^2 contribution	Unstandardized β (Lower, Upper)	r^2 contribution
Age	0.14** (0.05, 0.24)	0.11**	0.10 (-0.01, 0.20)	p = 0.07
Medications	0.57* (0.11, 1.02)	0.07*	0.51* (0.06, 0.96)	0.07*
Physical activity	Not entered		-0.007* (-0.014, -0.001)	0.12*
r	0.49		0.55	
r^2	0.24		0.30	
r^2 adj	0.21		0.26	

* p < 0.05, ** p < 0.01, ***p < 0.001 (n = 61)

Table 5.7 shows age and number of medications were retained in a model that explained 21 percent of the variance in STS5 performance. Slightly more of the variance (26%) was explained when PA was entered into the model containing age and number of medications. Notably, addition of PA resulted in age being relegated from the model.

5.3.7 Timed up-and-go multivariable regression analysis

The following variables were selected for multiple regression analysis of TUAG performance: age, diastolic blood pressure, C-reactive protein, albumin, troponin T, phosphate and comorbidity score. Serum creatinine, and number of medications had the lowest associations with task performance, and β coefficients (as well as confidence limits) which approached zero and were therefore not entered.

Table 5.8 Results of timed up-and-go multivariable regression analysis without and with physical activity as an additional predictor.

Variable	Unstandardized β (Lower, Upper)	Unstandardized β (Lower, Upper)	r^2 contribution
Diastolic blood pressure	-0.15** (-0.25, -0.05)	-0.15** (-0.25, -0.05)	0.08**
Albumin	-0.43** (-0.69, -0.17)	-0.43** (-0.69, -0.17)	0.10**
Troponin T	0.03*** (0.02, 0.05)	0.03*** (0.02, 0.05)	0.16***
Physical Activity	Not entered	-0.004(-0.009, 0.000)	(p = 0.065)
r	0.69	0.71	
r^2	0.48	0.51	
r^2 (adjusted)	0.45	0.48	

* p < 0.05, ** p < 0.01, ***p < 0.001 (n = 63)

Diastolic blood pressure, albumin and troponin T were retained in a model that explained almost 50% of the variance of TUAG performance (table 5.8). Whilst PA was moderately associated (r = 0.46, p < 0.001) with TUAG time at univariable level (β coefficient = -0.01 (-0.02, -0.01), p < 0.001), it was not retained as a predictor.

5.3.8 Incremental Shuttle Walk Test multivariable regression analysis

Ten variables were associated with ISWT of which, the following were entered for multiple regression analysis: age, BMI, number of medications, CRP, albumin, Troponin T, serum phosphate and creatinine. Number of medications was selected in preference to comorbidity number due to more favourable level of significance and stronger association with ISWT performance. Similar correlations were

observed for Troponin T and systemic pulse pressure with the ISWT and the former independent variables were moderately related to each other (r = 0.45, p < 0.001). Troponin T was selected for model entry following partial correlation analysis.

Table 5.9 Results of shuttle walk test distance multivariable analysis with physical activity (average daily activity counts) as additional predictor.

Variable	Unstandardized β (Lower, Upper)	r^2 contribution	Unstandardized β (Lower, Upper)	r^2 contribution
Age	-5.98*** (-8.85, -3.1)	0.22***	-3.57** (-6.09, -1.04)	0.06**
BMI	-8.62* (-15.54, -1.70)	0.07*	-6.91* (-12.59, -1.23)	0.04*
Medications	-17.3* (-31.1, -3.4)	0.05*	-11.5* (-22.6, -0.44)	0.03*
Physical Activity	Not entered		0.47*** (0.31, 0.64)	0.22***
r	0.63		0.79	
r^2	0.40		0.62	
r^2 adjusted	0.37		0.59	

* p < 0.05, ** p < 0.01, ***p < 0.001 (n = 61)

Age, BMI and number of medications were retained in a model that explained 37% of the variance. Physical activity was retained when added to this model and subsequently increased the amount of variance explained to 59%.

5.3.9 Self-reported functional status multiple regression analysis

Determinants of functional status were derived from multiple regression analysis of the following seven candidate variables some of which were similar for each outcome: gender; number of medications; albumin; predialysis creatinine; comorbidity score; serum parathyroid hormone; C-reactive protein. Number of medications and C-reactive protein were retained in a model, which explained almost a quarter of the variance of DASI scores. A trend was observed for gender (p = 0.052) and comorbidities (p = 0.059). Similarly, almost a quarter of the shared variance of PCS scores from the KDQOL-SF was explained by a model containing gender, albumin and comorbidities. The addition of PA resulted in a non-significant r^2 change of 0.01 and consequently did not increase the explanatory power of the model for the DASI questionnaire. In contrast, PA was retained in the model for the PCS at the expense of albumin, and subsequently increased the amount of variance explained to almost 30%.

Table 5.10 Results of self-reported functional status multivariable analysis with physical activity as additional predictor.

Variable	Duke activity status index †			KDQOL-SF Physical Component Score ††			
	Unstandardized β (Lower, Upper)	Unstandardized β (Lower,Upper)	r^2 contribution	Unstandardized β (Lower, Upper)	r^2 contribution	Unstandardized β (Lower, Upper)	r^2 contribution
Gender	-	-	-	-6.20* (-10.85, -1.55)	0.08*	-7.6** (-12.2, -2.9)	0.13**
Albumin	-	-		0.74* (0.20, 1.28)	0.10*	0.51(- 0.05, 1.07)	0.04, p = 0.08
Comorbidities	-	-		-3.66* (-6.39, -0.92)	0.07*	-2.8* (-5.58, -0.47)	0.05*
Medications.	-1.53* (-2.53, -0.53)	-1.37* (-2.39, -0.35)	0.12**	-		-	-
CRP	-0.35*(-0.64, 0.06)	-0.28* (-0.59, -0.03)	0.07*			-	
Physical Activity	Not entered	0.10 (-0.005, 0.025)	p = 0.18	Not entered		0.01* (0.001, 0.021)	0.06*
r	0.52	0.54		0.53		0.58	
r^2	0.27	0.29		0.28		0.34	
r^2 adjusted	0.23	0.24		0.24		0.29	

p < 0.05, ** p < 0.01, ***p < 0.001

† n = 63, †† n = 58

Table 5.11 shows that one quarter of participants undertaking physical performance assessments in the present study were classified as being frail overall according to criteria proposed by Fried et al. (2001) detailed in appendix (XXIX). One third to almost 90% of participants met individual frailty citeria derived via the outcomes employed in this study while less than 25% met the criteria for unintentional weight loss and low PA.

Table 5.11 Number (percentage) of study participants meeting frailty criteria for the overall score (frail) and each component, by group and gender.

	Frail (n = 73)	Weakness (n = 72)	Walking (n = 69)	Exhaustion (n = 69)	Low weight (n = 73)	Low PA (n = 63)
All	18 (24.7 %)	23 (31.9 %)	26 (37.7 %)	54 (78.3 %)	2 (2.7 %)	13 (20.6 %)
Men	12 (25.0 %)	15 (31.3 %)	17 (36.2 %)	34 (73.9%)	1 (2.1 %)	10 (25.0 %)
Women	6 (24.0 %)	8 (33.3 %)	9 (40.9 %)	20 (87.0 %)	1 (4.0 %)	3 (13.0 %)

5.4 Discussion

5.4.1 Physical performance characteristics of the study sample

Mean HGS values for men and women in the present study are consistent with those reported in larger samples of HD patients (Stenvinkel et al. 2002; Silva et al. 2011), and predialysis patients (Pagels et al. 2008). Notably, mean HGS for men and women was considerably lower (19% and 28% respectively) than age equivalent normative values and even lower (6% and 8% respectively) than healthy individuals aged over 70 years (Bohannon et al. 2006c). Sit-to-stand 5 times in the current study were slower than those reported by Blake and O'Meara (2004), whose high functioning HD participants were still 38% slower than healthy controls. Moreover, 41% of participants had a STS5 time equivalent or slower than normative data for people aged 70 - 79 years (12.6 seconds) (Bohannon 2006a). Timed up-and-go performances were slightly quicker than those reported for a more elderly sample (68.1 ± 7.1 years) of Japanese HD patients (Nonoyama et al. 2010). However, nearly 40% of our sample had TUAG times similar to those reported for adults aged 76 - 80 years (9.4 ± 2.4 years) (Bohannon 2006b; Pondal and del Ser 2008). Thirteen (21%) participants had TUAG results at the lower end of 'normal' (>12 seconds) mobility (Bischoff et al. 2003). Worryingly eight participants recorded

times greater than 13.5 seconds, which is an established cutpoint for predicting elderly fallers (Shumway-Cook et al. 2000).

The majority of participants (87%) had ISWT distances that were in the lowest 25th percentile reported for healthy middle-aged to older adults in the UK (Harrison et al. 2013). Shuttle walk performances were comparable to those reported for a similar aged sample (56.6 ± 12.2 years) of 128 UK HD patients (247.7m ± 137.1) (Greenwood et al. 2012) but generally worse than people with chronic heart failure (422 ± 119 metres) of comparable age (Pulz et al. 2008). Worryingly, 40% of participants had a maximum gait speed at test termination lower than the minimum speed required to walk across a UK pedestrian crossing safely (1.2 m/s) (Asher et al. 2012). Scores for the DASI were also consistent with those reported in previous stage 5 CKD studies (Nonoyama et al. 2010; Greenwood et al. 2012) and slightly lower than values for pre-dialysis patients (Kurella et al. 2004). Importantly, PCS scores from the KDQOL-SF were also in line with those reported in the DOPPS project, the largest international study involving people with stage 5 CKD (Lopes et al. 2007). As a comparison with normative data, 83% of participant PCS scores in the present study were at or below the 25th percentile of age-equivalent norm values (Ware et al. 2007). Physical activity level of men in particular was at least 12% lower than that reported for more senior adults (Hamer et al. 2012).

5.4.2 Overview of findings

The average age of the study sample was 57.5 (±15.5) years but results of physical performance testing indicated that a high percentage of participants had a level of functional capacity similar to adults of more advanced age (>70 years). Physical performance declined with factors typically associated with chronic illness such as advancing age, comorbidity burden, number of medications, and low PA. Although aspects of physical performance were correlated with some variables associated with stage 5 CKD, efficiency of uraemic toxin removal had no influence. Clinical and demographic variables explained between a quarter and half of the variance in functional capacity obtained via the implemented range of physical performance tests. In contrast, less than a quarter of the variance of self-reported functional status was explained by clinical and demographic characteristics. Physical activity emerged as the most influential determinant of a proxy measure of cardiorespiratory fitness (CRF) and was independently associated with lower limb function and self-reported functional status.

5.4.3 Hand-grip strength

Gender and albumin explained almost half of the variance in HGS most of which was contributed by the former. There is agreement that albumin is an important proxy marker of nutritional status in the HD population (Heimburger et al. 2000; Kaysen et al. 2000) which is also predictive of mortality (Lowrie and Lew 1990; Leavey et al. 2000). The independent association of albumin with HGS is consistent with previous studies documenting a similar relationship between this outcome and nutritional status of hospital inpatients (Norman et al. 2005) and protein-energy malnutrition among HD patients (Stenvinkel et al. 2002).

The model for HGS compares favourably with findings from the general literature showing age and gender as the principal determinants, accounting for around 30% of the variance of HGS in healthy individuals (Budziareck et al. 2008), older adults (van Lier and Payette 2003; Bot et al. 2012) and people with upper limb injury (Bot et al. 2012). None of these studies included markers of nutritional status as a candidate predictor variable, which may account for the discrepant findings. Notably, age was not associated with HGS at univariable level in contrast to the other physical performance measures. Further analysis revealed grip strength of female participants declined with advancing age but not in men. It is possible that males were more highly motivated and thus applied more effort to obtain better results, or despite adjustment for hand size the design of dynamometer was not suitable for women. It is perhaps more likely that this observation is due to onset of comparatively greater muscle capacity decline in women which is associated with menopausal transition (Carr 2003; Polotsky and Polotsky 2010).

5.4.4 Sit-to-stand 5

The modest amount of variance in STS5 performance explained by clinical and demographic variables here (26%) perhaps reflects the fact that knee extensor strength is the principal determinant of this task in community dwelling adults (Schenkman et al. 1996; Lord et al. 2002; Bohannon et al. 2010). This result is in keeping with a larger study of 669 community dwelling older adults, which found 10 variables (sensorimotor function indices, weight, pain) accounted for just 34.9% of the shared variance (Lord et al. 2002). Haemodialysis dosage and serum albumin explained a higher proportion of shared variance (46%) in a similar sample of HD patients (Johansen et al. 2001a), while Bohannon et al. (2007) found age and BMI accounted 43.7% in a larger sample of 94 community dwelling older adults. Notably,

PA completely attenuated the effect of age and was the principal predictor of STS5 performance in the present study. In contrast Johansen et al. (2001a) reported that PA was not independently associated with task outcome in their sample of HD patients. Participant characteristics for both studies were similar, but differences in statistical methods (forward versus backward stepwise regression, and treatment of PA data, Johansen et al. (2001a) quality control method not stated, and data not normalised to wear time) may have contributed to the disparity in findings. In addition, the cited study did not meet the minimum sample size requirement for multiple regression analysis recommended by Harris (1985).

Importantly, these data are consistent with results from the UK Medical Research Council National Survey of Health and Development which found self reported PA was independently associated with STS5 performance of 2400 adults (Cooper et al. 2011). Although, PA made the largest contribution to STS5 times, the amount of variance in task performance accounted for by the model was largely unchanged.

Notably, the number of prescription medications remained independently associated with STS5 performance and its relative importance was not attenuated by the introduction of PA to the model. Medication number has not been previously documented as a predictor of the STS5. Although this test has been proposed as a proxy measure of lower limb power (Guralnik et al. 1994), there is evidence that postural stability is the strongest determinant of chair rise time in older adults (Lindemann et al. 2007). Furthermore, chair rise performance is also associated with standing balance in middle-aged men (Hardy et al. 2010), and older adults with and without functional limitations (Schenkman et al. 1996; Lord et al. 2002). Taking three or more prescription medications is associated with an adjusted increased risk of impaired balance in older adults of at least 74% (Agostini et al. 2004). Worryingly, the median number of medications for participants in the present study was 10 (IQR = 8, 12). It is therefore speculated that number of medications may have independently contributed to STS5 performance via the vector of balance.

5.4.5 Timed up-and-go

The moderate amount of variance explained (48%) by albumin, diastolic blood pressure, and tropinin-T compares favourably with findings from the general literature. Kwan et al. (2011) reported that 43.5% of TUAG performance was determined by indices of sensorimotor function, balance, psychological and health measures with leg strength contributing the largest percentage in a sample of 280

older adults (>65 years). In contrast Pondal and del Ser (2008) found just 25.8% of the variance was explained by age, gender, weight, cognitive impairment and nutritional status in TUAG performances of elderly (>70 years) community dwelling adults.

The finding that a marker of nutritional status is a determinant of TUAG performance is in agreement with previous studies involving older adults showing mini-nutritional assessment is independently associated with TUAG times (Zeyfang et al. 2005; Ponda and del Ser 2008). The presence of albumin as a marker of nutritional status is a biologically plausible predictor of task performance. However, it is less clear why an index of heart refilling and a putative biomarker of cardiac muscle damage should account for the majority of the variance explained.

The TUAG correlated highly with the ISWT (Spearman's rho = -0.85, $p < 0.001$), which suggests that similar factors may influence both tests although the TUAG is a short test of functional mobility and not CRF. Participants are exposed to an orthostatic challenge during the sit-to-stand transfer, which elicits an immediate increase in heart rate followed by an initial drop in blood pressure (Olufson et al. 2008). Retention of cardiac related variables might be considered consistent with short-term cardiovascular regulation in response to an orthostatic challenge. This is likely impaired in stage 5 CKD a condition characterised by reduced cardiovascular function (London et al. 2011).

Notably, while PA was related to TUAG times at univariable level, it was not retained as a predictor in the final model due to the presence of Troponin T. This finding is surprising as B-natriuretic peptide expression (a biomarker of ventricular stress) was observed to be lower in maintenance HD patients following a structured PA programme (Toussaint et al. 2008a). It is possible that this negative result may be due to heteroscedasticity of the PA data.

5.4.6 Incremental Shuttle Walk Test

Explanatory power of the model for the ISWT containing age, BMI, and number of medications was significantly improved when PA was added as a predictor. Moreover PA explained a greater proportion of the variance than the other three variables combined. The same predictors explained a similar amount of the variance for gait speed at test termination and CRF in METs calculated from gait speed (appendices XXIII a and XXIII b). Johansen et al. (2001) and Kutsuna et al. (2010) also found that PA was a determinant of self-selected gait speed of HD patients,

which is correlated with CRF. Approximately 60% of the variance in ISWT performance was explained by age, BMI, number of medications and habitual PA in the present study. This is less than the model of Probst et al. (2012) who reported age, gender and BMI explained 71% of the variance in ISWT results of 246 healthy middle-aged adults. This discrepancy may be due to advanced age of participants in the present study and perhaps also psychosocial factors associated with a long-term condition, which may have affected motivation. Notably median self-perceived exertion score at test termination was just 13, which equates to 'somewhat hard' on the BORG scale while a score of 20 indicates maximum exertion (Borg 1998).

Medication number emerged as a predictor of test performance, which is plausible in light of the influence of polypharmacy on standing balance (Agostini et al. 2004). Moreover, a high percentage of participants (78%) were prescribed heart pacing and/or antihypertensive medications. Presence or absence of medications such as β blockers has previously been reported as a predictor of CRF of similar age patients referred for hospital based exercise testing (Roy et al. 1992; Myers et al. 2001). Notably, average heart rate at test completion (as a percentage of predicted maximum) for participants was lower than the study of Probst et al. (2012) (64% versus 99% respectively).

Overall, the model for the ISWT (a proxy measure of aerobic fitness) is in agreement with previous research showing age, body composition and PA are the principal drivers of CRF in healthy adults across a similar age range (Jackson et al. 1990; Matthews et al. 1999; Jurca et al. 2005). Moreover, the amount of variance in directly measured CRF explained by non-exercise predictive equations developed from these studies (58% to 74%) is comparable to the present study.

5.4.7 Functional status – DASI and KDQOL-SF physical component score

Overall, clinical and demographic variables explained a modest amount of the variance in self reported physical function. Gender, albumin and comorbidity number made a similarly important contribution to summary physical component scores of the KDQOL-SF. Clinical and demographic variables explained a similar amount of the variance in KDQOL-SF physical function subscale scores (28.9%) in a combined sample of 146 HD and peritoneal dialysis patients (Carmichael et al. 2000). Importantly, these results are consistent with findings from the much larger DOPPS study, which found gender, comorbidity status, albumin and age were independently associated with PCS scores (Lopes et al. 2007). Addition of PA slightly increased

the amount of variance explained and subsequently forced albumin from the model while at the same time attenuating the effect of comorbidity number. Interestingly, post-hoc analysis revealed the independent contribution of PA was mediated by a substantial main effect for gender. Although cause and effect cannot be established in a cross-sectional study, this finding suggests that functional status of males only may potentially be modified by habitual PA.

The DASI questionnaire contains items weighted according to their approximate physiological cost, and scores are reported to correlate moderately with directly measured CRF (Struthers et al. 2008; Hlatky et al. 1989). Therefore it might be expected that determinants for the DASI would be similar to the ISWT. Medication number was a shared predictor of both outcomes, but it is less clear why the contribution of other factors notably PA was supplanted by polypharmacy when the influence of the latter on ISWT distance was attenuated by PA. Previous studies have identified combinations of age, sex, comorbidity score and history of heart failure as determinants of DASI scores in larger samples of middle-aged and elderly cardiac patients (Nelson et al. 1991; Jaeger et al. 1994). Furthermore, a relatively low amount of the variance in scores was explained but this is in agreement with a study of 438 middle aged cardiac patients, which accounted for just 18% of the variance in DASI scores (Nelson et al. 1991).

The disparity in explanatory ability between the models for physical performance and self-reported functional status likely reflects a number of key differences. Physical performance tasks and self-report questionnaires assess different aspects of physical function from the ICF framework (functional capacity versus functional status). Second, comparatively lower reliability of self-reported physical function (Davey et al. 2003; Overend et al. 2010) will likely attenuate relationships between independent variables and questionnaire outcomes. Day of the week and method of administration are reported to influence questionnaire scores (Weingberger et al. 1996; Lyons et al. 1999; Nelson-Danquah et al. 2010). Third, psychosocial factors influence both physical performance and self-reported function but its relative importance to the latter may arguably be greater (Carmichael et al. 2000; Lord et al. 2002; Bean et al. 2011). Anecdotally, some participants expressed concern regarding the purpose of the questionnaires (in particular the DASI) despite reassurances of confidentiality. Almost half of participants (44%) required state sponsored support for subsistence living due to their health condition. It is speculated that such concerns may have impacted validity of some questionnaire

answers thereby constituting a form of bias, which can account for up to one third of total response bias (Sjöström et al. 1999).

5.4.8 Physical activity an important determinant of physical function

These data are in agreement with observations from the general literature documenting positive independent associations between self-reported PA and self-reported function of middle aged adults (He and Baker 2004; Lahti et al. 2010) and objectively measured function of middle-aged adults (Lang et al. 2007). Independent association between objectively measured PA and self-selected gait speed of maintenance HD patients, which is similarly predictive of health outcomes has been previously reported (Johansen et al. 2001a; Kutsuna et al. 2010). Crucially, habitual PA was the principal modifiable determinant of ISWT and STS5 performance. This is important because the former is a proxy measure of CRF which is predictive of mortality in stage 5 CKD (Sietsema et al. 2004) while the latter has discriminative ability in identifying HD patients with fractures (Jamal et al. 2006). These outcomes are arguably also corrolaries of the two core components of frailty: exhaustion and weakness (Fried et al. 2001). Furthermore, adjusting for PA level either removed or attenuated the influence on physical performance capability of other predictors such nutritional status, medication number, and BMI. Notably, the latter has been employed as a proxy for unintended weight loss, another core component of frailty.

This is the first study to document habitual PA as a determinant of PCS score from the KDQOL-SF, a measure of self reported physical function which is widely used in this clinical population. Importantly, there is a growing emphasis on patient-reported outcomes to complement traditional clinical outcomes such as mortality, non-fatal events, hospital admissions, and healthcare cost (Liem et al. 2007; Valderas et al. 2008). However, it appears that only a small proportion of functional status may be directly influenced by the physiological effects of PA. Hand-grip strength was not associated with PA but this finding concurs with large scale studies of middle aged and older adults (Cooper et al. 2011; Rapp et al. 2012) and is likely due to hip mounted accelerometers not capturing upper limb activity. Overall, these data point to habitual PA as the modifiable factor of greatest relative importance for physical performance of this sample of HD patients. Importantly, this suggests a significant proportion of outcomes important in frailty and survival are mediated by a decline in habitual PA, which is reported to be on average 3.4% per month following HD commencement (Johansen et al. 2003b).

5.4.9 Nutritional status and physical function

Higher serum albumin was independently associated with better HGS, TUAG performance and PCS score, and was moderately associated with the ISWT at univariable level. These data are in agreement with those of Johansen et al. (2001a), indicating nutritional status as a determinant of physical function of HD patients. There is considerable evidence that albumin and inflammation are closely linked in CKD (Johansen et al. 2003c; Kalentar-Zadeh et al. 2003; Fouque et al. 2008) particularly in uraemic individuals with protein energy malnutrition (Stenvinkel et al. 2002; Kaizu et al. 2003; Castaneda-Sceppa et al. 2007; Carrero et al. 2008). In the present study inflammation (C-reactive protein) correlated moderately with albumin (Spearman's rho = -0.40, p = 0.001) as well as physical function.

Renal failure and HD therapy have both been implicated in decreased protein synthesis and increased protein degradation in people with stage 5 CKD (Ikizler et al. 2002; Raj et al. 2008). Muscle morphology changes observed in malnutrition are well documented with muscle biopsies showing selective atrophy of type II muscle fibres (anaerobic, glycolytic, fast twitch) (Norman et al. 2010). Notably, HD patients exhibit significant atrophy of all muscle fibre types compared to non-uraemic peers (Sakkas et al. 2003). As well as mediating a preferential loss of whole body protein from muscle mass (Heymsfield et al. 1982), malnutrition is believed to impair muscle function by causing fatigability and an altered pattern of muscle contraction and relaxation (Lopes et al. 1982).

Simultaneous monitoring of serum potassium and magnesium levels was not undertaken in this study. However, the effect of electrolyte disturbances characteristic of stage 5 CKD (ie: hyperkalaemia) on functional capacity via impaired muscle membrane function should be considered. Elevated serum potassium is implicated in muscle fatigue during exercise (Sjested and Sjogaard 2000; Fraser et al. 2002) and is inversely associated with CPET measured CRF in stage 5 CKD (Sangkabutra et al. 2003). Reduced muscle sodium-potassium adenosine triphosphatase (ATPase) activity observed in uraemic rats (Bonilla et al. 1991) is believed to occur in humans (Brearley et al. 1993) and thus partly mediate impaired extrarenal potassium regulation. Hypermagnesaemia is extremely rare, however, hypomagnesaemia affects five percent of HD patients (Alhosaini and Leehey 2015) and may also adversely affect skeletal muscle membrane function as deficiency of this cation reduces sodium-potassium ATPase activity (Alhosaini and Leehey 2015).

Additionally, β-adrenergic agonists often prescribed to manage blood pressure in stage 5 CKD elevate serum potassium levels (Kullmer and Kindermann 1985).

5.4.10 The role of muscle mass, uraemia severity and anaemia

Intuitively, muscle mass might be expected to be a determinant of physical function as it is linearly related to strength in healthy young and older adults (Overend et al. 1992; Newman et al. 2003; Rolland et al. 2008). Moreover, muscle strength is a predictor of physical performance of HD patients (Diesel et al. 1993). Although serum creatinine (employed as a gross marker of sarcopenia) was modestly associated with physical function it was not retained as an independent predictor, which is inagreement with the findings of Johansen et al. (2001a). Serum creatinine is largely determined by muscle mass in HD patients (Noori et al. 2011) but it is an indirect measure that may not reflect muscle architecture changes that occur in uraemic individuals (Ahonen 1980; Diesel et al. 1993; Johansen et al. 2003a; Sakkas et al. 2003). Higher fat infiltration of skeletal muscle and reduced contractile area are associated with lower muscle strength and reduced physical performance of HD patients (Johansen et al. 2003a) and older adults (Goodpaster et al. 2001; Visser et al. 2002; Visser et al. 2005; Delmonico et al. 2009). Although BMI is commonly used as an adiposity surrogate, recognised limitations in reflecting body composition (Pasco et al. 2012) may explain why it was not correlated with non-endurance tasks.

It has been proposed that declining physical function in CKD is largely mediated by uraemia (Diesel et al. 1993; Johansen et al. 2001a; Kurella et al. 2004; Brodin et al. 2008). However, while condition-related variables (albumin and inflammation) were associated with physical function, dialysis adequacy was not. This result contrasts with a previous study, which found dialysis dosage (KT/v) was an independent predictor of physical performance (Johansen et al. 2001a). It is possible that use of urea reduction ratio as a measure of dialysis adequacy in the present study instead of Kt/V may explain the divergent results. However, larger studies have found no association between HGS and Kt/V, or other dialysis-related biomarkers (Qureshi et al. 1998; Leal 2011). Moreover, no independent association between renal function and PCS scores was found in people with stage 3 to 5 CKD (Perlman et al. 2005).

Partial correction of anaemia with erythropoiesis-stimulating agents is reported to significantly improve cardiopulmonary exercise test (CPET) measured CRF and self-reported physical function of maintenance HD patients (Johansen et al. 2010).

However, haemoglobin and haematocrit level were not associated with physical performance outcomes and only weakly associated with DASI scores. This result concurs with previous studies showing no association between haematocrit and VO_2peak of anaemic HD patients (Diesel et al. 1993) or functional capacity of individuals with partially corrected anaemia (Johansen et al. 2001a). Taken together it appears that physical function in this sample of HD patients was neither influenced by efficiency of uraemic toxin removal nor anaemia status *per se*. Instead, factors related to stage 5 CKD and indeed most long-term conditions (age, nutritional status, polypharmacy, PA) made a greater relative contribution.

5.4.11 Clinical implications and further research

As a whole these findings show there are a number of risk factors for low physical function across a range of physical function attributes in this sample of people with stage 5 CKD, many of which are potentially modifiable. Importantly habitual PA emerged as a determinant of function, which appeared to attenuate the influence of other predictors (ie: nutritional status, BMI, medications, age). Thus, strategies aimed at improving PA level and carefully managing the number of prescribed medications may likely improve physical performance outcomes, which are predictive of falls, fractures and premature mortality of people with CKD and older adults. Encouraging PA among maintenance HD patients is part of KDOQI recommendations for managing CV risk in this population (NKF 2005). Clearly, these data indicate PA has an equally important role in helping arrest the inexorable decline towards frailty that many people experience after starting HD therapy.

There is ample evidence from the general literature supporting the nomothetic utility of functional status questionnaires, which arguably have greater relevance to disability and quality of life of people with stage 5 CKD than clinical indices of health. In addition, they can be completed by those unable, or too reticent to undertake physical performance testing. However, recognised shortcomings regarding reliability, response bias and appropriateness for patients with cognitive deficits (Guralnik et al. 1989) may limit their clinical utility. Furthermore, self-reported functional status was largely determined by factors other than clinical or demographic factors and habitual PA in this sample of HD patients. Consequently, more research is required before clinicians can invest in self-report measures and rely on the evidence provided by these outcomes for the benefit of their patients. If functional status is to be used as a primary outcome to monitor health and evaluate

PA health interventions it should not be used in isolation but in tandem with objective measures of functional capacity.

The aim of this study was to explore the importance of routinely monitored demographic and clinical information as potential determinants of physical function as well as the relative importance of habitual PA as a behavioural variable. Around half the variance of physical performance and three quarters of the variance in functional status remains undetermined. Future studies may seek to address the contribution of psychosocial factors such as pain and fatigue, which were not investigated in this study but are known to be predictors of physical performance (van Lier and Payette 2003; Brown et al 2005; Bot et al. 2012).

The ISWT was employed in this study as a proxy measure of CRF, which is predictive of mortality in the CKD population (Sietsema et al. 2004; Gulati et al 2012). However, there are indications that ISWT distance may not be a good predictor of event free survival in CHF patients (Pulz et al. 2008). If this field test of CRF is to be adopted into clinical practice in line with KDOQI recommendations regarding monitoring of physical function, research is required to determine the predictive utility of the ISWT against CPET measured VO_2peak.

Hand-grip strength has been proposed as a simple physical function marker which reflects nutritional status of people with stage 5 CKD and mortality risk (Stenvinkel et al. 2002). However, although HGS is strongly associated ($r = 0.77$, $p < 0.001$) with total body protein measured directly by *in vivo* neutron activation analysis (Windsor and Hill 1988), the relative contribution of albumin to HGS was small. Moreover, there is currently no consensus threshold of HGS to define whether someone is normal or malnourished or at risk of premature mortality. Further research is warranted if HGS is to be employed diagnostically in the HD population.

Medication number was implicated in physical performance but the individual influence of particular medications frequently used for cardiovascular management of stage 5 CKD patients, such as angiotensin converting enzyme (ACE) inhibitors and statins may be as important. Angiotensin enzyme polymorphisms influence skeletal muscle phenotype and functional properties in older adults as well as athletes (Lima et al. 2010; Gineviciene et al. 2011; Seto et al. 2011; Costa et al. 2012). Furthermore, large-scale studies indicate that ACE inhibitors are independently associated with preservation of lower limb muscle mass and knee extensor strength of adults (Onder et al. 2006). Conversely, adverse effects of

cholesterol modifying drugs may include statin-induced myopathy (Tomaszewski et al. 2011). Exploration of commonly prescribed medications on phenotypic expression of genes associated with skeletal muscle response to PA is suggested.

5.4.12 Limitations

As this was a cross-sectional study definitive conclusions regarding causality cannot be made regarding the variables associated with the physical function outcomes investigated. Physical function measures were obtained from a single visit, which may have been influenced by acute fluctuations of mood, symptoms and/or health status (Nelson-Danquah et al. 2010). Repeated measures of physical function analysed as a time-dependent covariate would likely yield a more robust effect estimate for the multivariable models. At least one longitudinal study has however demonstrated an independent association between self-reported PA and functional status (SF-36 PCS) of middle-aged adults (Lahti et al. 2010). Moreover, there is agreement from several literature reviews that physical function of HD patients is significantly improved following structured PA programmes (Parsons and King-van Vlack 2009; Kosmadakis et al. 2010; Segura-Orti 2010; Smart and Steele 2011).

Analyses were undertaken on a sample of self-selected participants while physical performance of individuals ineligible or unwilling to participate was undetermined. Although the percentage of female participants closely reflects the UK HD population (UKRR 2012) men made up the greater proportion of the sample. Therefore, these results should be generalised with caution to the wider HD population and may not be generalised to non-ambulatory patients.

The study sample size fulfilled the minimum requirement for multiple regression analysis outlined by Harris (1985) but it was lower than the threshold recommended by Tabachnick and Fidell (2007) of 50 + 8(k) (where k is the number of independent variables). In addition, a limitation of stepwise regression is that it may be prone to overfitting the data, for example the model may fit better on the participant sample in which it was developed compared to individuals from outside the sample. This issue may be attenuated if the criterion for retaining a candidate variable is robust enough and is the reason why backward rather than forward stepwise regression was chosen in this analysis. Larger-scale prospective studies are recommended to support the validity of models reported in the present study.

5.5 Conclusion

In light of the potential predictive ability of both subjective and objective measures of physical function, routine monitoring of these outcomes has been recommended to assist the management of this long-term condition. Importantly, the observations made in the current study indicate that several clinical and/or demographic factors related to stage 5 CKD influence physical function but overall PA appears to be the most important modifiable risk factor. Findings from this study therefore underscore the importance of current KDOQI guidelines encouraging the promotion of PA among people with stage 5 CKD to augment medical management. Moreover, early intervention is recommended to prevent what appears to be an inexorable decline towards frailty and poor outcomes once CKD severity requires HD therapy. Further research is also indicated regarding the predictive utility of field tests of physical performance if these outcomes are to be recommended as adjunct measurements alongside traditional clinical outcomes. Physical function questionnaires investigated in this study do not appear to be suitable for individual patient monitoring.

What is known about this topic:

- People with CKD 5 have significant impairment of physical function.
- Physical function is predictive of health outcomes in this population.
- Factors associated with a chronic condition and haemodialysis dosage are determinants of physical function of maintenance HD patients
- Regular monitoring of physical function is recommended as part of condition management.

What this study adds:

- Efficiency of dialysis therapy *per se* does not influence physical function.
- Physical activity underpins aspects of physical performance in stage 5 CKD.
- Self-reported functional status of HD patients is heavily influenced by factors other than physical activity, demographic and clinical indices.
- Further research regarding the prognostic utility of physical performance tests of functional capacity in stage 5 CKD is indicated.

Chapter 6: Correlates of arterial stiffness in stage 5 CKD

6.1 Introduction

6.1.1 Background

Advances in medical management have incrementally improved the first year survival outlook of incident dialysis patients, however long term prognosis is bleak. Five-year survival rates are as low as 35% (UKRR 2010; USRDS 2010; Breidhardt et al. 2011; SRRR 2013) and life expectancies for people undergoing maintenance dialysis therapy aged over 50 years are reduced six fold compared to non-uraemic peers in the general population (UKRR 2012). High mortality is mediated largely by cardiovascular disease, which accounts for around 36 - 50% of deaths among maintenance HD patients (UKRR 2010; USRDS 2010; SRRR 2011). Alarmingly, incident cardiovascular (CV) events are at least three times higher among people with stage 5 CKD compared to the general population (Parfrey et al. 1996; Go et al. 2004; Tonelli et al. 2006).

6.1.2 Cardiovascular mortality and arterial stiffness.

Atherosclerosis, which is characterized by occlusive lesions of the intima is only partially responsible for high CV morbidity and mortality in stage 5 CKD (London et al. 2002). A large proportion of increased CV risk has been attributed to arteriosclerosis, which affects the media layer of the aorta and large conduit arteries and increases vessel stiffness (London et al. 2002; Stenvinkel et al. 2008; London et al. 2011; Verbeke et al. 2011). Increased central arterial stiffness is believed to be the principal mechanism for isolated systolic hypertension (London et al. 1996; O'Rourke and Hashimoto 2007). The principal outcomes of chronically high systolic afterload are left ventricular hypertrophy (LVH) (Marchais et al. 1993; Toprak et al. 2009), which is present in 75% of HD patients (Foley et al. 1995; Nitta et al. 2004) and impaired coronary perfusion during diastole (O'Rourke and Hashimoto 2007; Wang et al. 2007). Importantly, elevated blood pressure, diastolic dysfunction and LVH are independent predictors of CV morbidity and mortality of maintenance HD patients (Silberberg et al. 1989; Parfrey et al. 1996; Iseki et al. 1997).

Carotid femoral pulse wave velocity (PWV), which is a surrogate measure of aortic artery stiffness is independently predictive of CV and all cause mortality among people with stage 5 CKD (Blacher et al. 1999; London et al. 2001a; Verbeke et al. 2011). Moreover, it is similarly predictive of outcomes for people with hypertension

(Laurent et al. 2006), diabetes (Cruickshank et al. 2002) and older adults (Sutton-Tyrell et al. 2005). Importantly, the predictive utility of PWV is independent of traditional and novel CV risk factors (Vlachopoulos et al. 2010). Augmentation index (AI) is another non-invasive vascular measure, which calculates the impact of wave reflections from the vascular periphery on the ascending aortic pressure waveform (O'Rourke and Kelly 1993). Wave reflections and aortic stiffness contribute to isolated systolic hypertension (London et al. 2001a) and are both independently associated with increased left ventricular mass of HD patients (Avolio et al. 1983; Marchais et al. 1993). Considered a composite measure of arterial stiffness, AI is also predictive of CV mortality among patients undergoing percutaneous coronary interventions (Weber et al. 2005) and HD patients independent of aortic PWV (London et al. 2001a).

Although arterial stiffening is a pathophysiological process that is driven by advancing age (Benetos et al. 2002; Blacher et al. 2003; O'Rourke and Hashimoto 2007), accelerated vascular aging is a putative phenotype of CKD 5 (Pannier et al. 2005; London et al. 2011). Mechanisms involved in accelerated arterial stiffness are incompletely understood, however, pathogenesis is believed to be mediated largely by accelerated calcification of the media layer of central and conduit arteries (Blacher et al. 2001; Raggi et al. 2007; Sigrist et al. 2007; Temmar et al. 2010). Gender, blood pressure, diabetes, medications and genetic polymorphisms have also been associated with arterial stiffness (Blacher et al. 2003; Yasmin et al. 2006; Achimastos et al. 2007) but relatively few studies have explored the role of behavioural factors such as physical activity (PA).

6.1.3 Arterial stiffness and physical activity

Accumulating evidence indicates PA that improves or maintains cardiorespiratory fitness (CRF) attenuates age attendant vascular stiffening of adults of all ages (Vaitkevicius et al. 1993; Tanaka et al. 2000; Boreham et al. 2004; Aoyagi et al. 2010; Gando et al. 2010b). There are also indications that light PA is beneficial in attenuating arterial stiffness of older adults (Gando et al. 2010a). Moreover, physical inactivity negatively impacts endothelial function and biological mechanisms which regulate vascular tone and contribute to remodeling of the arterial wall (Wang 2005; Green et al. 2004; Suvorava et al. 2004; Thijssen et al. 2009; Whyte and Laughlin 2010). Importantly, stage 5 CKD is characterised by high prevalence of sedentary behaviour and low CRF (Johansen et al. 2000; Longenecker et al. 2002; Stack et al.

2005; Cupisti et al. 2010; Tentori et al. 2010) both of which are implicated in premature mortality (O'Hare et al. 2003; Sietsema et al. 2004; Matsuzawa et al. 2012). Current KDOQI guidelines recommend encouraging PA among HD patients as part of cardiovascular health management (NKF 2005). However, there is a little data regarding the potential relationship between intermediate vascular endpoints that are predictive of mortality in stage 5 CKD and PA and CRF.

6.1.4 Summary

Despite advances in medical management of CKD 5 statistics highlight low survival outcomes due to disproportionately high CV morbidity and mortality. Increased arterial stiffness is proposed as one of the mechanisms responsible for CVD mortality among maintenance HD patients. Physical activity and CRF are implicated in longevity of maintenance HD patients and there is general consensus that PA which improves aerobic fitness directly benefits arterial health. However, there is presently a paucity of research exploring both behavioural and clinical correlates of arterial stiffness indices of maintenance HD patients.

The objectives of this study were to:

- Explore clinical and demographic correlates of indices of arterial stiffness of people with stage 5 CKD.
- Explore the relationship between objectively measured physical activity and aerobic fitness and indices of arterial stiffness of people with stage 5 CKD.

6.2 Methods

6.2.1 Study design, participant recruitment, inclusion/exclusion criteria

The present study was conducted in accordance with the ethical principles described in the Declaration of Helsinki. Ethical approval was obtained from the West of Scotland Research Ethics Committee and the Monklands Hospital Research and Development Department. This was a cross-sectional cohort study involving 73 self-selected volunteer participants, aged >18 years, ambulant with or without a walking aid, and undergoing maintenance HD therapy for stage 5 CKD. Participants were recruited from an NHS outpatient HD unit at Monklands Hospital, Airdrie. Participants were screened by their physician to verify their eligibility for safe participation in the study. The following exclusion criteria were applied: pregnancy; unstable cardiovascular conditions, recent cerebrovascular event; recent pulmonary thromboembolism; excessive inter-dialytic weight gain determined by physician; use of corticosteroids and anabolic therapies; recent pulmonary embolism; serum potassium >6 mmol/L; infection or course of antibiotics within one month of study period. Individuals were ineligible if they had been diagnosed with dementia/severe cognitive impairment, or were not fluent in written and spoken English. Written informed consent was obtained from each participant prior to study commencement.

6.2.2 Demographic and clinical measures

Anthropometric and clinical measures (age, height, weight, BMI, resting heart rate, resting blood pressure) were taken prior to assessment of physical performance (general methods 2.1.3). Mean arterial pressure (MAP) was calculated using equation 6.1.

Equation 6.1 Mean arterial pressure

$$MAP = \text{diastolic BP} + [(\text{systolic BP} - \text{diastolic BP})/3]$$

(London et al. 2001a)

The following biochemistry measures were extracted from participants' electronic records of their most recent pre-dialysis blood tests (general methods 2.6.1): dialysis adequacy (urea reduction ration), haemoglobin, haematocrit, C-reactive protein, albumin, serum phosphate, corrected serum calcium, parathyroid, pre-dialysis creatinine. Other variables included a simple additive score of comorbidity, which was obtained from review of electronic hospital records (general methods 2.8.1).

6.2.3 Measurement of arterial stiffness.

Carotid femoral pulse wave velocity (PWV) and augmentation index (AI) measurements were determined using a Vicorder (Skidmore Medical Ltd, Bristol). Assessment conditions were controlled as carefully as practicable (general methods 2.2.2, table 2.1) and measurements were taken on a non-dialysis day with participants lying in a standardized position. Brachial blood pressure was obtained using an AND Model UA-767 digital oscillometric blood pressure monitor (A&D instruments Ltd, Oxfordshire) after 15 minutes of complete rest (general methods 2.2.1). Triplicate PWV and AI measurements were obtained as per general methods sections 2.2.2 and 2.2.3. Aortic PWV was calculated by the Vicorder software using equation 6.2, while AI was determined from brachial artery pressure wave forms via a transfer function performed by the Vicorder software. Data regarding number of vasoactive medications for each participant was recorded (general methods 2.7.1) and explored as potential candidate variable in subsequent data analysis.

Equation 6.2 Pulse wave velocity
PWV = aortic path length (suprasternal notch to top of thigh cuff) divided by pulse wave transit time

6.2.4 Assessment of cardiorespiratory fitness

A proxy measure of peak CRF was obtained from a symptom limited incremental shuttle walk test (ISWT) as per general methods section 2.3.4. Participants' heart rate response was monitored (general methods 2.3.4.1) throughout and the test was terminated according to (ACSM 2010) guidelines for exercise testing (general methods 2.3.4.4). Distance walked and perceived level of exertion according to the BORG scale (appendix II) at test termination were recorded.

6.2.5 Assessment of physical activity

Estimates of PA were obtained via triaxial accelerometry (general methods 2.5.1) using the Actigraph GT3X (Actigraph Corp, Pensacola, Florida). Participants kept a wear log (appendix V b). The Actigraph was worn over an eight day period (general methods 2.5.7) and retrieved on day 9 coinciding with a routine HD appointment. Actigraph PA data were reduced as per general methods sections 2.5.3 and 2.5.4. Only those participants with a minimum of eight hours monitor wear on one dialysis day and two non-dialysis days were included for final analyses (as per recommendations of chapter 3).

6.2.6 Data analysis.

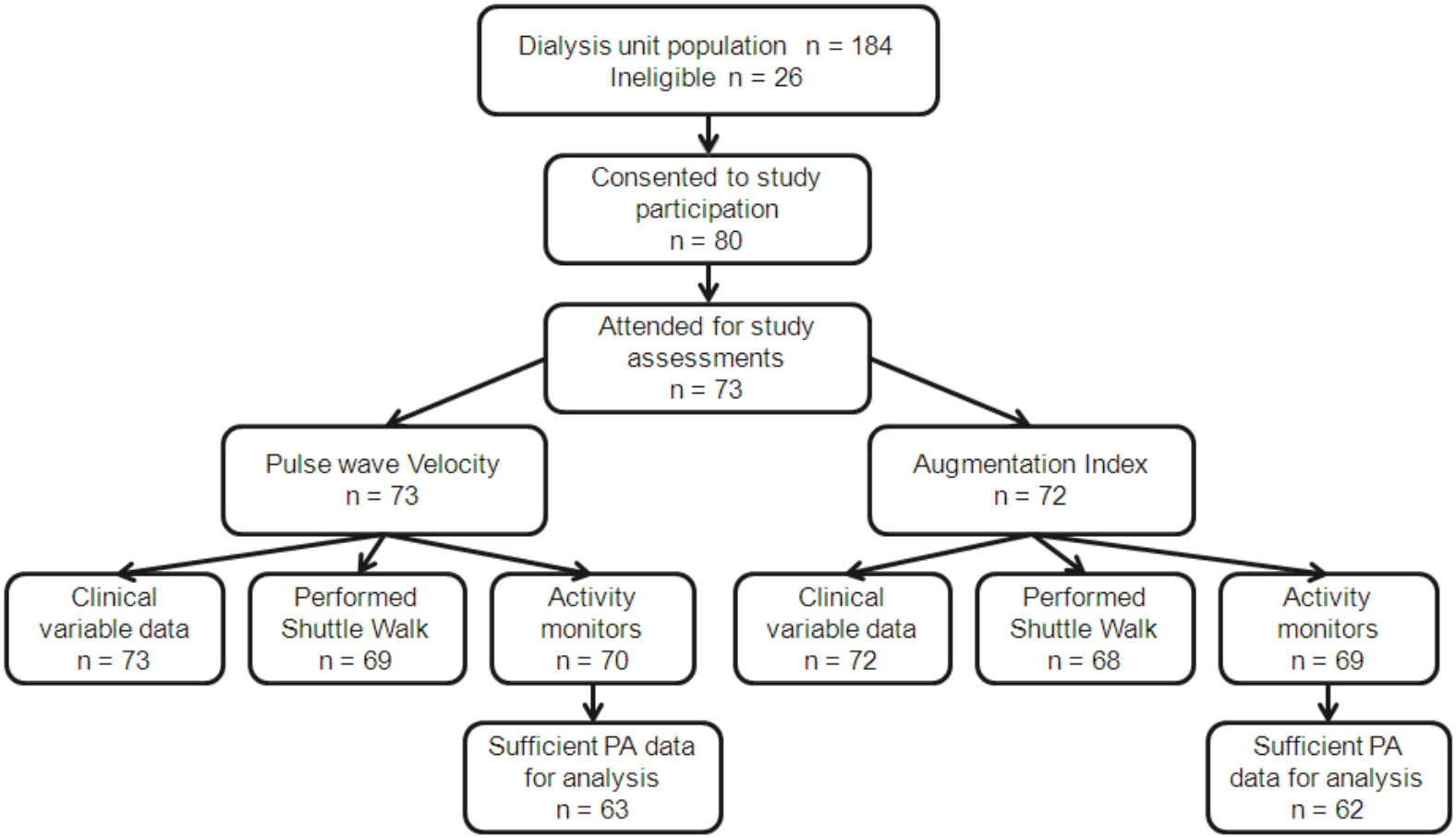
Data analysis was undertaken using the Statistical Package for Social Science (SPSS, Illinois, USA), version 19.0. Sample characteristics are presented as mean and standard deviation (SD) or median and interquartile range according to results of normality testing (Kolmogorov-Smirnov). Differences between groups for the same variable were tested using an independent t-test or Mann-Whitney U test for normal and non-normal data respectively. Univariable regressions between arterial stiffness indices and demographic and clinical variables were performed. Variables associated with arterial outcomes, which had a correlation of >0.20 and a significance level of ≤0.05 were identified as candidate predictor variables. If the minimum ratio of variables to sample size for multiple regression analysis recommended by Harris (1985) was violated a selection process was employed to reduce the number of variables. Variables were not selected for entry to the multiple regression analysis if their β coefficient and confidence intervals approached zero. If variables exhibited collinearity, partial correlation analysis was used to select the most robust variable for model entry. Backward stepwise regression analysis was used with the selected candidate variables. Physical activity was subsequently added to the model containing only the retained clinical and demographic variables. Statistical significance for multiple regression analysis was set at a two-tailed value of $p < 0.05$. Adjusted r^2 values are also reported (Altman 1995).

6.3 Results.

6.3.1 Participation.

Eighty people initially agreed to take part in the study. Seven people either did not attend their appointment or withdrew their consent for this study. Seventy three people underwent measurement of arterial stiffness and participated in the physical activity and physical performance part of the study. A measure of AI was unable to be obtained for one participant. Of those who participated in the vascular stiffness measures four people declined the shuttle walk test and three participants declined or were unable to wear the Actigraph. Another seven participants lacked sufficient accelerometer wear time for final analyses as defined by the recommendations of chapter three. Figure 6.5 illustrates patient participation and inclusion for multiple regression analyses.

Figure 6.1 Flowchart of patient participation and inclusion for multiple regression analyses.



6.3.2 Sample characteristics

Demographic and clinical characteristics for participants with minimum required monitor wear time are reported in table 6.1 and are not significantly different to the initially recruited sample of 72 participants (appendix XXIV).

Table 6.1 Demographic and clinical characteristics of all participants (n = 73). Data are presented as mean ± SD, or median (IQR) for normal and non-normally distributed data respectively.

Characteristic	
Age *(years)*	55.6 ± 15.6
Gender *M/F (%)*	48/25
Weight	81.0 ±17.5
Height	167.7 ± 16.6
Body Mass Index *(kg/m^2)*	28.5 ± 6.3
Resting Heart rate *(bpm)*	72.0 ± 13.0
Systolic *(mmHg)*	135.6 ± 24.5
Diastolic *(mmHg)*	77.6 ± 12.0
Systemic pulse pressure *(mmHg)*	52 (43 - 70)
Mean arterial pressure *(mmHg)*	96.9 ±13.8
Haemodialysis Vintage *(months)*	16.8 (6.7 - 32.7)
Renal Replacement Therapy Vintage *(months)*	25.9 (8.1 - 68.8)
Haemoglobin *(g/dL)*	11.2 ± 1.0
Haematocrit *(%)*	33.9 ± 3.2
C-reactive protein *(mg/L)*	0 (0 - 10.0)
Dialysis Adequacy *(%)*	71 (66 - 75)
Albumin *(g/L)*	39.0 (36.0 - 42.0)
Troponin T *(ng/L)*	37 (20.5 - 69.5)
Corrected Calcium serum level *(mmol/L)*	2.36 ± 0.17
Phosphate *(mmol/L)*	1.43 ± 0.41
Parathyroid level *(mmol/L)*	16.8 (9.9 - 30.6)
Creatinine pre-dialysis *(µmol/L)*	683 (558 - 672)
Number of vasoactive medications	2.0 (1.0 - 3.5)
Number of comorbidities, *(N)*	1.0 ± 0.8
• Hypertension *(%)*	42 (58)
• Diabetes mellitus *(%)*	16 (22)
• Cardiovascular disease *(%)*	14 (19)
Pulse wave velocity (m/s)	7.5 (6.3 - 9.0) 8.03 ± 2.3[†]
Augmentation Index (%) [¥]	20.4 ± 7.5
Shuttle walk test distance (metres)[∞]	280 (170 - 440)
Physical activity (based on daily average Triaxial cpm) [€]	289 (183 - 397)

[†]data non-normally distributed, mean ± SD presented for comparison

[¥]n = 72, [∞]n = 69, [€]n = 63

Participant age ranged from 24 to 87 years, with 35 percent of the sample aged 65 years or older. Participants with diagnosed diabetes accounted for 22 percent and women made up 34 percent of the sample. The average age of female participants (49.9 ± 13.1 years) was significantly younger ($t(71) = 2.33$, $p = 0.02$) than males (58.6 ± 16.1 years).

Average measure intra-class correlation coefficients for intra-session measurements of PWV and AI were 0.99 (0.987 - 0.994) and 0.95 (0.919 - 0.964) respectively. The average intra-subject coefficient of variation for intra-session PWV was 3.1% and 13% for AI. Non-parametric testing revealed PWV values for women were significantly lower than those for men for both the whole sample ($U = 404$, $p = 0.02$, $n = 73$) and the reduced sample of participants with sufficient PA data ($U = 311$, $p = 0.03$, $n = 63$). Diabetic participants also had significantly higher PWV than non-diabetics ($U = 187$, $p < 0.001$) and there was no significant difference in age between the two groups ($U = 363$, $p = 0.22$). Independent t-tests revealed no significant gender differences in AI values for the whole sample ($t(70) = -0.61$, $p = 0.55$) and the reduced sample size of participants with sufficient PA data ($t(60) = -0.13$, $p = 0.90$). Similarly, there were no significant differences in AI values between diabetic and non-diabetic participants ($t(70) = -0.22$, $p = 0.83$).

Table 6.2 Arterial stiffness, physical activity and CRF status according to gender.

Outcome	Men (n = 48)	Women (n = 25)
Pulse wave velocity	8.4 ± 2.4[†]	7.3 ± 2.0[†]
	8.1 (6.7 - 9.9)	6.7 (6.2 - 8.0)
Augmentation Index	20.0 ± 7.9[¥]	21.1 ± 6.7
Shuttle walk test distance *(m)*	270 (160 - 480)[¥]	335 (168 - 408)[£]
Physical activity (Triaxial cpm)	245 (147 - 387)[∞]	322 (259 - 450)[€]

[†] Data not normally distributed mean ± SD presented for comparison.

[¥]n = 47 ,[∞]n = 40, [€]n = 23, [£]n = 22

6.3.3 Univariable analyses

Eleven clinical and demographic variables were significantly associated with PWV at univariable level for the sample of participants (table 6.3). The strongest association was observed between age and PWV (Pearson's $r = 0.63$, $p < 0.001$), while more modest associations were seen with the remaining clinical variables. Univariable

analysis yielded similar associations when performed on the participant sample with sufficient PA data for final analyses (appendix XXV a). Some slight changes were observed, for example, associations with diabetic status, troponin-t, serum phosphate, number of vasoactive medications, serum creatinine (postdialysis) and ISWT weakened slightly. In addition, associations with gender and comorbidities were no longer significant. Correlations with, age and HD vintage were slightly stronger, although the coefficient for the latter was lower, which could potentially reduce the contribution of this variable in a multivariable regression model.

Table 6.3 Univariable associations with pulse wave velocity.

n = 73	Unstandardized β (Lower, Upper)	r^2
Age	0.09*** (0.07, 0.12)	0.40***
Systolic blood pressure	0.05*** (0.03, 0.07)	0.25***
Troponin-t	0.012** (0.005, 0.019)	0.14**
Diabetic status	1.92** (0.71, 3.14)	0.12**
Vasoactive Medications	0.44** (0.14, 0.74)	0.12**
Phosphate	-1.86** (-3.10, -0.61)	-0.11**
Creatinine (predialysis) †	-0.003* (-0.005, 0)	-0.07*
Creatinine (postdialysis) †	-0.006* (-0.011, -0.001)	-0.07*
HD Vintage	0.022* (0.004, 0.04)	0.07*
Comorbidities	0.75* (0.09, 1.41)	0.07*
Gender	-1.12* (-2.21, -0.02)	-0.06*
Shuttle walk (m) ∞	-0.004*** (-0.006, -0.002)	-0.20***
Physical activity (cpm)	-0.003*(-0.005, -0.001)	-0.09**

*p < 0.05, ** p < 0.01, ***p < 0.001

†n = 71, ∞n = 69, €n = 63

Fewer demographic and clinical variables were related to AI compared to PWV (table 6.4) and with more modest associations typically observed. Although the proxy measure of aerobic fitness (the ISWT) was significantly associated with this index of arterial stiffness, PA was not (p = 0.22).

Table 6.4 Significant univariable associations with augmentation index.

n = 72	Unstandardized β (Lower, Upper)	r^2
Height	-0.14** (-0.24, -0.04)	-0.10**
Age	0.14* (0.03, 0.25)	0.09*
BMI	0.34* (0.071, 0.61)	0.08**
Heart rate (resting)	-0.16* (-0.29, -0.03)	0.08**
Haematocrit †	0.64* (0.11, 1.17)	0.08*
Haemoglobin	1.713* (0.101, 3.326)	0.06*
Shuttle walk (m) ∞	-0.009* (-0.017, -0.002)	0.09**
Physical activity (cpm)	-0.005 (-0.012, 0.003)	0.05, p = 0.11

*p < 0.05, ** p < 0.01, ***p < 0.001

†n = 71, ∞n = 68, €n = 62

Results of univariable analysis performed with data for participants with sufficient activity monitor wear time were again similar. Slightly lower β coefficients and stronger correlations were observed for the following variables: age, height, ISWT, (appendix XXV b). However, associations with BMI and haematocrit were no longer significant and a slightly stronger association was observed for resting heart rate. Notably, no significant association was observed between PWV and AI for participants with values for both outcomes (n = 72) and those with the sufficient PA data (p = 0.15 and p = 0.38 respectively).

6.3.4 Pulse wave velocity multivariable regression analysis.

The following candidate variables were entered for multivariable regression analysis with PWV as the dependent variable: age, number of vasoactive medications, diabetic status, serum phosphate, troponin T, HD vintage, systolic blood pressure, gender. Post-dialysis serum creatinine was selected over predialysis serum creatinine as the coefficient limits for the latter included zero.

Table 6.5 Results of pulse wave velocity multivariable regression analysis with resulting model subsequently adjusted for PA and CRF level.

	PWV Model (n = 73)	PWV Model adjusted for PA (n = 63)	PWV Model adjusted for CRF (n = 69)
Variable	Unstandardized β (Lower, Upper)	Unstandardized β (Lower, Upper)	Unstandardized β (Lower, Upper)
Age	0.07*** (0.05, 0.10)	0.082*** (0.056, 0.108)	0.07*** (0.05, 0.10)
Troponin-T	0.006* (0.001, 0.011)	0.003 (-0.003, 0.009)	0.005* (0, 0.011)
HD vintage	0.014* (0.001, 0.026)	0.013 (-0.001, 0.027)	0.014* (0, 0.027)
Systolic Bp	0.036*** (0.021, 0.05)	0.036*** (0.02, 0.053)	0.035*** (0.020, 0.051)
Physical Activity	Not entered	0 (-0.002, 0.002)	0 (-0.002, 0.002)
r	0.79	0.77	0.78
r^2	0.62	0.59	0.61
r^2 (adjusted)	0.60	0.57	0.59

*p < 0.05, ** p < 0.01, ***p < 0.001

Over half of the variance in PWV values was explained by systolic blood pressure, HD vintage, troponin-T, and age (table 6.5). The addition of habitual PA level effected no significant change in the explained shared variance and was not significant in the model (p = 0.72). In addition, troponin-T was no longer independently associated with PWV (p = 0.27) and HD vintage was reduced to a trend (p = 0.06). In contrast the model remained unchanged after adjustment for CRF level (ISWT performance) and the latter was not retained as a significant predictor (p = 0.76).

6.3.5 Augmentation index multivariable regression analysis

On the basis of preliminary univariable analyses the following six candidate variables were entered for multiple regression analysis for AI: age, height, haematocrit, haemoglobin, BMI and resting heart rate.

Table 6.6 Results of augmentation index multivariable regression analysis with model subsequently adjusted for PA and CRF level.

	AI model (n = 72)	AI model adjusted for PA (n = 61)	AI model adjusted for CRF (n = 67)
Variable	Unstandardized β (Lower, Upper)	Unstandardized β (Lower, Upper)	Unstandardized β (Lower, Upper)
Age	0.11* (0.01, 0.20)	0.08 (-0.02, 0.18)	0.12* (0.02, 0.22)
Height	-0.14** (-0.23, -0.04)	-0.11* (-0.21, -0.02)	-0.13** (-0.23, -0.04)
BMI	0.36** (0.11, 0.61)	0.29* (0.02, 0.55)	0.37** (0.12, 0.63)
Heart rate (rest)	-0.20** (-0.32, -0.08)	-0.25*** (-0.38, -0.12)	-0.19** (-0.32, -0.07)
Haemoglobin	1.42* (0.03, 2.82)	1.25 (-0.34, 2.83)	1.28 (-0.21, 2.76)
PA	not entered	0.001 (-0.01, 0.01)	-0.002 (-0.01, 0.01)
r	0.63	0.53	0.62
r^2	0.39	0.28	0.39
r^2 (adjusted)	0.35	0.24	0.34

*p < 0.05, ** p < 0.01, ***p < 0.001

One third of the variance in AI values was explained by age, height, BMI, and resting heart rate, with the latter making the largest relative contribution (table 6.6). Subsequent adjustment for PA level did not improve the model and the former was not retained as a predictor of AI (p = 0.86). In addition, when the sample size was reduced to only those individuals with sufficient PA data for analysis, age was no longer independently associated with AI and the variance explained consequently decreased. The addition of CRF level (ISWT performance) effected no significant change in the explained shared variance from the initial AI model and was not significant (p = 0.63).

6.4 Discussion

6.4.1 Contextualising this sample of people with stage 5 CKD

The average age of participants in the present study was broadly similar (either the same or up to four years higher) compared to mortality and exercise intervention studies with vascular outcomes previously undertaken in stage 5 CKD (London et al. 1992; Blacher et al. 1999; London et al. 2001a; Blacher et al. 2003; Mustata et al. 2004; Koh et al. 2010). The only exception being the study by Toussaint et al. (2008a) in which participants were at least a decade older. Length of time on dialysis in previous studies is difficult to compare as mean rather than median HD vintage are commonly reported despite standard deviations, which clearly indicate data are not normally distributed.

Compared to previous vascular health studies undertaken in stage 5 CKD, participants in the present study demonstrated generally lower values for similar arterial stiffness indices. Average PWV values were at least 11% lower than those reported in exercise intervention studies (Toussaint et al. 2008a; Koh et al. 2010) and 7 to 30% lower than previous vascular health and mortality studies undertaken in stage 5 CKD (London et al. 1992; Blacher et al. 1999; London et al. 2001a; Shoji et al. 2001; Avramovski et al. 2013). Augmentation index values were similar to those reported by Koh et al. (2010) but 12% lower than those of London et al. (1992). However, average AI values in the present study were nearly one third lower than those reported for CKD patients not requiring renal replacement therapy (RRT) (Mustata et al. 2010), and HD patients in the exercise intervention study of Toussaint et al. (2008a). In addition, blood pressure indices for participants in the present study were at least 5% lower compared to earlier arterial stiffness studies involving people with stage 5 CKD (Blacher et al. 1999; London et al. 2001a; Toussaint et al. 2008a; Koh et al. 2010). Taken together it appears that participants in the present study have generally better vascular health as measured by indices of arterial stiffness compared to other samples of maintenance HD patients.

Average measure intra-class correlation coefficients for the PWV and AI measures were both excellent. Coefficient of variation for PWV values obtained by the Vicorder in the present study (3.1%) was comparable to the 2.8% reported by Hickson et al. (2009) and 5% reported by Shoji et al. (2001) for the SphygmoCor device. Reassuringly it is also much lower than the 22% reported by van Leeuwen-Segarceanu et al. (2010). The coefficient of variation for AI was 13%, which is

substantially higher than the 2.4% reported for AI measures obtained by SphygmoCor in healthy adults (Covic et al. 2000).

6.4.2 Overview of findings

The data from the current study concur with previous reports that age, and blood pressure are the principal drivers of the characteristic aortic artery stiffness of maintenance HD patients. Novel findings were that HD vintage and a biomarker of cardiac damage were also retained in a statistical model which accounted for over half of the variance in PWV values. Commonly reported determinants of AI including age, height and heart rate were also found to be independent predictors of AI in the present sample of maintenance HD patients. Just under a third of the variance was explained by a model, which also included serum haemoglobin and BMI as novel independent predictors of AI. Although PWV and time to the reflection point are thought to be the principal determinants of AI (Rossi et al. 2011) no significant association was observed between these vascular indices. Habitual PA and CRF were correlated with arterial stiffness at univariable level but neither emerged as an independent predictor in the multivariable analyses.

6.4.3 Independent predictors of arterial stiffness

6.4.3.1 Age and blood pressure

Age and brachial systolic blood pressure appear to explain the majority of shared variance when entered separately into the PWV model. This is in agreement with a large body of studies reporting age and blood pressure indices as important PWV risk factors in larger and smaller cohorts of maintenance HD patients (Shoji et al. 2001; Blacher et al. 2003 and Temmar et al. 2010 respectively), people with CKD not requiring RRT (Temmar et al. 2010) and a systematic review of 77 studies (Cecilja and Chowienczyk 2009). The physiological basis for age attendant increase in arterial stiffness is believed to be due to changes in the extracellular matrix of the arterial wall. Elastin cells are gradually lost or become calcified (Yu and Blumentahl 1963) and there is an overproduction of abnormal collagen cells which start to form crosslinks (Greenwald 2007). In addition, degradation and fragmentation of the elastin lamellae from repetitive stress cycles subsequently places greater load on stiffer collagen fibres and changes arterial diameter (Benetos et al. 2002). Age perhaps represents the least modifiable risk factor for increased arterial stiffness. However, whether changes in the arterial wall extracellular matrix are due to the

aging process *per se* or associated with long-term exposure to other risk factors for vascular aging such as diabetes and blood pressure is uncertain (Chue et al. 2010).

The independent association of systolic blood pressure with PWV in the present study is also consistent with overwhelming evidence highlighting blood pressure as a determinant of aortic stiffness in people with and without CKD (Laurent et al. 2005; Cecilja and Chowienczyk 2009). According to the Maxwell model, as transmural pressure rises and distends the artery there is progressively greater recruitment of collagen fibres and a concomitant reduction in elasticity (Bank et al. 1996). In addition, the role of hypertension in hypertrophy of the arterial media to maintain tensile stress within physiological limits (Laplace's law) is well documented (Benetos et al. 1993; Dobrin 1995; Safar and Frohlich 2007). Wall thickness, elastic modulus, and vessel diameter are the principal factors in the Moens–Korteweg equation to calculate PWV. Importantly, elevated blood pressure is also inversely associated with endothelial function (Nigam et al. 2003), which provides functional regulation of aortic stiffness via vasomotor control (McEniery et al. 2006; Bruno et al. 2012). Indices of blood pressure were not associated with AI, which is in agreement with a previous study involving maintenance HD patients (London et al. 1992) and studies of hypertensive humans and animals (Safar et al. 2000). Moreover, there is evidence of a blood pressure independent association between AI and the ratio of extra cellular to intracellular fluid in CKD 5 (Lin et al. 2003).

6.4.3.2 Haemodialysis vintage

Haemodialysis therapy emerged as an independent risk factor for aortic arterial stiffness while dialysis adequacy was not correlated. Hotta et al. (2012) similarly observed HD vintage was correlated with brachial-ankle PWV ($r = 0.32$, $p < 0.05$). This result suggests that length of exposure to stage 5 CKD requiring HD therapy is a more important risk factor for vascular aging than efficiency of uraemic solute removal. There is consensus that accelerated vascular aging occurs in the presence of uraemia (London et al. 1990; London et al. 1992; Pannier et al. 2005; Avramovski et al. 2013) but this is the first time the relative contribution of exposure to HD therapy has been quantified. Worryingly, just six years of HD was needed to increase PWV by 1 m/s and thus mortality risk by 15% compared to 14.3 years of chronological age. No relationship was found between HD vintage and AI, which is surprising as this index is correlated with endothelial function which is also independently associated with HD vintage (Cheng et al. 2008). Progressive

concentric LVH occurs among maintenance HD patients (Foley et al. 2010) and contribution of HD vintage to increased arterial stiffness is a plausible reason why this happens. It is debatable whether this risk factor for aortic stiffness is modifiable, but the fact that total RRT vintage was not associated with PWV suggests it may be. Aortic stiffness appears to be ameliorated following kidney transplantation (Covic et al. 2003; Posadzy-Malaczynska et al. 2005) or its progression at least slowed (Zoungas et al. 2004; Bachelet-Rousseau et al. 2011). Whether this is due to lifestyle change or reversal of uraemia *per se* and improved blood pressure control (Bachelet-Rousseau et al 2011), reduced inflammation (Lima et al. 2011, Simmons et al. 2005) as well as favourable effects of restored prostaglandin synthesis on vascular tone is unclear.

6.4.3.3 Troponin-T

More regularly used as a biomarker for diagnosing acute coronary episodes, Troponin-t emerged as an independent predictor of PWV. Baia et al. (2011) also found high sensitivity Troponin-t was independently associated with PWV in older adults. It is more likely that this variable is an expression of the upstream effects of arterial stiffness rather than an influencing factor. Mechanistically, increased aortic stiffness is believed to result in faster incident and early return of reflected waves, which increase aortic and left ventricular pressure during systole (London et al. 1996; O'Rourke and Hashimoto 2007). This result indicates that subsequent chronic increases in systolic stress not only cause deleterious changes in ventricular morphology and function (Marchais et al. 1992; Toprak et al. 2009) but also subclinical myocardial damage. Interestingly, these data indicate that aortic arterial stiffness but not wave reflections is a mediator of myocardial injury. This result suggests that a reduction in PWV may be more likely to reduce subclinical myocardial damage in this group of people with stage 5 CKD.

6.4.3.4 Heart rate and arterial stiffness

Resting heart rate was inversely associated with AI which is in agreement with findings from large-scale epidemiological studies (Janner et al. 2010; Chirinos et al. 2011) and studies exploring AI response to heart rate induced by ventricular pacing (Stefanadis et al. 1998), atrial pacing (Wilkinson et al. 2000; Wilkinson et al. 2002) and dobutamine (Sharman et al. 2009). Mechanistically, it has been proposed that a faster heart rate shortens systole duration resulting in the reflected wave being shifted towards diastole thereby lowering height of the second systolic peak and

thus augmentation pressure (Wilkinson et al. 2002). It has also been suggested that there is a shortening of the rapid phase of ventricular ejection and consequently a reduction in ejection velocity (Wilkinson et al. 2002). However, wave reflections still return during systole with a higher heart rate suggesting shifts in wave form timing may not be the principle driving factor in AI (Sharman et al. 2009). Notably, an increase of 10 beats per minute equated to an incremental 2% reduction in AI in the present study. Larger incremental reductions were reported in the ACCT (McEniery et al. 2005) and heart rate manipulation studies (Wilkinson et al. 2000; Wilkinson et al. 2002) (5% and 4% respectively). The lower coefficient observed here may be due to the large percentage of participants on heart pacing medications.

In contrast, resting heart rate was not a correlate of PWV in the present study but it has previously been independently associated with PWV of HD patients (Blacher et al. 2003) and healthy adults (Achimastos et al. 2007). The coefficient and univariable r^2 for heart period reported by Blacher et al. (2003) were both very small (β = -0.0039 and r^2 = 0.02, $p < 0.001$) and differing findings may be due to the comparatively smaller size of this study and thus lower statistical power to detect an association. However, studies specifically examining the effect of heart rate on PWV have shown that while changes in heart rate are inversely associated with ejection duration, aortic PWV is not affected (Wilkinson et al. 2000; Wilkinson et al. 2002).

6.4.3.5 Haemoglobin and haematocrit and augmentation index

Haematocrit and haemoglobin level were both correlates of AI with the latter retained as an independent predictor, which has not been previously reported. Although this result is novel, it may be considered consistent with studies demonstrating a significant increase in peripheral resistance and mean arterial pressure of maintenance HD patients following partial correction of anaemia (Steffen et al. 1989; Mayer et al. 1991). An increase in peripheral resistance would likely increase wave reflections and thus AI. Anaemia instead induces an ‘anoxic’ peripheral vasodilatory effect (Nichols and O’Rourke 2005), which would likely reduce the amplitude of retrograde pressure waves and augmentation pressure.

6.4.3.6 Height and augmentation index

Stature was independently and inversely correlated with AI which is in agreement with studies demonstrating wave reflections occur later in taller individuals (Smulyan et al. 1998; McGrath et al. 2001). Taller stature and concomitant greater effective length of the arterial system lengthens the distance to the reflection point, thereby

extending the time interval for the reflected wave. London et al. (1995) reported higher AI in their female participants was associated with shorter height and greater tapering of the abdominal aorta compared to men. In the present study males were significantly taller than female participants ($U = 67.5$, $p < 0.001$), however, no gender difference in AI values was found. The effects of shorter stature may have been partially offset by greater distensibility of peripheral arteries in younger women compared to men (London et al. 1995). Another suggested explanation is the influence of heart rate on AI. In small mammals a shorter time to the reflection point is paralleled by a shorter heart period (increased heart rate) to maintain optimal ventricular/vascular coupling (London et al. 1995). As resting heart rates of females were significantly higher than male participants ($t(70) = 2.17$, $p = 0.03$) this might account for why gender did not influence AI values despite differences in stature.

6.4.3.7 Body mass index and augmentation index

Body mass index was independently associated with AI in the present study, which has not been previously reported for stage 5 CKD patients. An increase of 5 kg/m^2 resulted in an incremental increase of 1.8 % in AI values, which is in keeping with a 1.5% increase ($p = 0.004$) observed by Shim et al. (2011) for overweight older women. Body mass index is independently associated with declining endothelial function of peritoneal dialysis patients (Cheng et al. 2008), which is suggested as one of the mechanisms by which AI is influenced. Persistent mild inflammation, which is associated with obesity due to higher levels of pro-inflammatory cytokines released from adipose tissue (Fain 2006) may impair endothelial function and increase vascular tone. Endothelial function represents the functional component of arterial stiffness and is inversely associated with AI of healthy individuals (Nichols and O'Rourke 2005) and diabetics (Ravikumar et al. 2002). Another potential player is angiotensin II, which is observed to exert a greater vasoconstrictive response in adults with visceral obesity (Nielsen et al. 2004).

Insulin resistance and hyperglycaemia related to obesity is also a plausible mechanism. Higher circulating levels of fatty acids and glucose may mediate an increase in nonenzymatic glycation of arterial wall collagen cells (Airaksinen et al. 1993). Lastly, leptin released from adipose tissue is implicated in proliferation and migration of vascular smooth cells (Oda et al. 2001) and arterial calcification (Parhami et al. 2001). Moreover, this hormone is associated with arterial distensibility independent of endothelial function (Singhal et al. 2002).

6.4.4 Contextualisation of derived arterial stiffness prediction models

The amount of PWV variance explained in the present study (60%) is similar to previous stage 5 CKD studies of Blacher et al. (2003) and Temmar et al. (2010) (57% and 49% respectively). It is also in line with results reported in large-scale studies of healthy adults (51% to 58%) by Yasmin et al. (2006) and Achimastos et al. (2007). Age, height, BMI and resting heart rate were independently associated with AI with which is consistent with findings from large epidemiological studies of apparently healthy individuals (van Trijp et al. 2004; Janner et al. 2010; Chirinos et al. 2011). The amount of variance explained in the present study (35%) sits near the middle of a wide spectrum of results reported in the general literature which range from 19% to 73% (van Trijp et al. 2004; Chirinos et al. 2011). It is considerably less than the 58% reported for a mixed cohort of HD patients and controls (London et al. 1992). However London et al. (1992) did not undertake subgroup analysis for participants with stage 5 CKD which may have yielded a different result. A larger subsequent study by the same research group involving only HD patients (London et al. 2001a) accounted for a lower amount of AI variance (49%) but still more than the present study. Although age of the study groups was similar, in the latter study the percentage of diabetic participants taking part was less than half that of the present study (10%). In addition, heart rate was used as the chronotropic variable in this study while both cited studies used left ventricular ejection duration. Sharman et al. (2009) reported that substitution of ejection duration for heart rate significantly improved their AI prediction model by a further 7%. Differing methods of wave form assessment and transfer functions may have also contributed to differing results. Previous studies employed doppler or SphygmoCor devices and tonometry of the radial artery while the Vicorder used in the current study employs oscillometry for wave form sampling of the brachial artery.

Age was an important independent predictor of PWV in the current study, a fact that is well documented in the general literature (Cecilja and Chowienczyk 2009). The adjusted coefficient for age (β = 0.073) was similar to that reported by Blacher et al. (2003) in a larger study of 242 maintenance HD patients (β = 0.079) and the ACCT (β = 0.078) involving 1000 healthy participants (McEniery et al. 2005). In contrast, Temmar et al. (2010) and Townsend et al. (2010) reported higher coefficients for HD patients and people with CKD not requiring RRT (β = 0.15 and 0.11 respectively). Participants in these studies were on average six to 10 years older, which may account for some of this difference as the relationship between PWV and age

increases in strength with advancing age (Mitchell et al. 2004; McEniery et al. 2005; Janner et al. 2010). Notably the largest coefficient reported in a larger sample of HD patients (β = 0.33) was by Shoji et al. (2001). The reason for the large disparity is unclear but may relate to the lower shared variance explained by their model (r^2 = 27, $p < 0.001$) and a higher proportion of female participants compared to the present study (59% versus 33% respectively).

Age appeared to make a comparatively more modest independent contribution to AI when entered separately to the model (r^2 change = 0.05, $p < 0.05$). Stronger univariable associations between age and AI are reported in the general literature (r = 0.41 to 0.58, $p < 0.01$) for younger adults (Kelly et al. 2001; Lemogoum et al. 2004; Binder et al. 2006) than that observed here. Differing results may be due to important differential effects of age on these vascular indices. Findings from large-scale studies such as the ACCT, Framingham Heart Study and the Copenhagen City Heart Study report curvilinear relationships between AI, PWV and age (Mitchell et al. 2004; McEniery et al. 2005; Janner et al. 2010). Augmentation index increases with advancing years until age 40 - 50, after which a plateau is observed, while the relationship between age and PWV increases after this point (McEniery et al. 2005; Janner et al. 2010).

6.4.5 Correlates of arterial stiffness

6.4.5.1 Gender

Male gender was positively associated with PWV at univariable level but it was not retained as an independent predictor, which is in agreement with previous studies involving people with stage 5 CKD (London et al. 1992; Shoji et al. 2001; Beerenhout et al. 2003; Temmar et al. 2010) and healthy individuals (Vaitkevicius et al. 1993). In contrast, studies involving larger cohorts of HD patients (Blacher et al. 2003), people with CKD not requiring RRT (Townsend et al. 2010) and healthy adults (McEniery et al. 2005; Achimastos et al. 2007) have reported gender as a determinant. Pulse wave velocity values for women in the present study were significantly lower than those for men, however the former were on average 8.7 years younger, which may explain why gender was not a predictor after adjustment for age. Gender was not independently associated with AI in the present study, which is in line with a study of HD patients and controls by London et al. (1992). In contrast large epidemiological studies of apparently healthy individuals have reported gender as a determinant of AI (Janner et al. 2010; Chirinos et al. 2011).

Central arterial stiffness of premenopausal women is generally lower than men and is attributed to the influence of gender-related sex steroid hormones (Rossi et al. 2011). However, gender differences in vascular stiffness rapidly diminish after menopause (Waddell et al. 2001; Mitchell et al. 2004).

Differing findings regarding the independent influence of gender on arterial stiffness may possibly be attributed to the presence of CKD, which interrupts normal hormonal function. Interestingly, although over half of the women in this study would be classified as premenopausal (<50 years) (Rymer and Morris 2000) a Mann-Whitney U test revealed no significant gender difference in PWV values for participants aged <50 years ($U = 78$, $p = 0.56$). This suggests that either the beneficial vascular effects of female hormones may have been nullified by CKD related factors, or early onset of menopause which has also been reported in the HD population (Shanmugavadivoo and Shaariah 2003; Song et al. 2008).

6.4.5.2 Diabetic status

Diabetic participants were similar in age to non-diabetics ($U = 363$, $p = 0.22$) but demonstrated significantly higher PWV values ($U = 187$, $p < 0.001$), which is in agreement with a larger study of 265 maintenance HD patients (Shoji et al. 2001). Diabetes is believed to increase arterial stiffness via hyperglycaemia driven accumulation of advanced glycolated end products (AGEs), which mediate structural change in artery walls (Lakatta 2003; Konova et al. 2004). Another likely pathway is via inflammation induced endothelial dysfunction commonly observed with diabetes (Naka et al. 2012; Ravikumar et al. 2002; Tan et al. 2002), which elicits changes in arterial tone as well as structure. Numerous studies using a range of methodologies agree that diabetes is characterized by increased arterial stiffness throughout the vascular tree across all ages (Stehouwer et al. 2008).

Despite being significantly correlated with PWV, diabetes did not emerge as an independent predictor in the current study in contrast to previous studies of people with CKD (Shoji et al. 2001; Temmar et al. 2010; Townsend et al. 2010). This discrepancy may be due to a smaller percentage of diabetic participants (22%) here compared to the cited studies, in which diabetics made up between one third to a half of participants. In addition, diabetic status and systolic blood pressure were moderately correlated (Spearman's rho = 0.51, $p < 0.001$) and adjustment for the latter completely attenuated the association between diabetes and PWV ($r = 0.09$, p

= 0.44). It is suggested that higher blood pressure observed with diabetic status is probably why PWV was observed to be higher among diabetics in the present study.

Surprisingly, AI and diabetic status were not correlated and there was no significant difference in AI values between diabetic and non-diabetic participants ($t(70) = 0.22$, $p = 0.83$). These results add to a growing body of studies which agree that aortic stiffness is higher in diabetics, but that a concomitant differential increase in AI does not necessarily occur. Values are either no different (Westerbacka et al. 2000; Ravikumar et al. 2002; Lacy et al. 2004; Schram et al. 2004) or lower (Cheng et al. 2007) compared to controls. Crucially, diabetes is independently associated with higher CV mortality among HD patients (Shoji et al. 2001). Lack of association between diabetic status and AI is difficult to reconcile and raises doubt over its validity in a population characterised by high prevalence of this condition.

6.4.5.3 Paradoxical and absent correlations

Inflammation, high serum levels of phosphate and activation of the renin-angiotensin system are some of the putative mechanisms for increased arterial stiffness in stage 5 CKD. Inflammation is significantly associated with CV risk and mortality among maintenance HD patients (Zimmerman et al. 1999; Shoji et al. 2001) but it was not correlated with PWV or AI ($p = 0.09$ and $p = 0.22$ respectively). Use of a high sensitivity assay of CRP may have yielded a different result. However, the weight of evidence suggests that inflammation has more profound influence on endothelial dysfunction (Fichtlscherer et al. 2000) and morphological changes to the arterial intima (Stenvinkel et al. 1999; Torzewski et al. 2000; Zoccali et al. 2000) than the tunica media. Importantly, arterial stiffening is driven largely by pathological changes in the latter (Blacher et al. 2001; London et al. 2003). Moreover, CRP is reported to be predictive of CV and all cause mortality among HD patients independent of aortic PWV (Shoji et al. 2001). Stage 5 CKD is independently associated with AI and PWV (London et al. 1992), however, efficiency of uraemic solute removal (URR) was not correlated with either index. This result suggests that uraemia *per se* does not mediate increased arterial stiffness of maintenance HD patients. It is possible that this may be because by the time dialysis is commenced at least 50% of patients show some degree large artery calcification (Guerin et al. 2001; Sigrist et al. 2006) a proportion that increases up to almost three quarters among prevalent HD patients (Chesterton et al. 2005; Sigrist et al. 2006).

Higher serum phosphate is implicated in aortic calcification in stage 5 CKD (Jono et al. 2000; Moe and Chen 2004) and is associated with CV and all-cause mortality in this population (London et al. 2005; Melamed et al. 2006). Paradoxically, serum phosphate, calcium and calcium phosphate product were inversely associated with aortic PWV. The reason for this is unclear as treatment of hyperphosphataemia with phosphate binders has been found to slow progression of aortic calcification (Chertow et al. 2002). Notably, Melamed et al. (2006) observed a higher mortality risk among HD patients whose phosphate levels declined over six months and suggested this may have been due to aggressive use of phosphate binders. No correlations were observed between serum parathyroid hormone and arterial stiffness indices. This result is consistent with a current lack of consensus in the literature regarding the contribution of these biomarkers to arterial calcification and mortality in stage 5 CKD (London et al. 2005; Melamed et al. 2006).

Serum creatinine was inversely associated with PWV, which is at odds with a longitudinal study of treated hypertensives showing this biomarker was the most important determinant of PWV over six years (Benetos et al. 2002). In addition, number of vasoactive medications was positively related to PWV, while a trend was observed for ACE inhibitor use ($r = 0.18$, $p = 0.06$). The reason for latter is unclear as meta-analyses of ACE inhibitor use demonstrate modulation of the renin-angiotensin system lowers arterial stiffness (Safar et al. 2004; Ong et al. 2011).

6.4.5.4 Which index of blood pressure?

In the current study, systolic blood pressure was independently associated with PWV in agreement with studies of healthy adults (Achimastos et al. 2007; Ronnback et al. 2007; Naka et al. 2012) and diabetics (Naka et al. 2012). However, MAP which represents the steady component of blood pressure and the main arbiter of arterial wall stress according to Laplace's law is the most commonly reported predictor of PWV in HD studies (Beerenhout et al. 2003; Blacher et al. 2003; Temmar et al. 2010) and people with CKD not requiring RRT (Townsend et al. 2010). Although MAP was a determinant of PWV in previous HD studies it was not a significant correlate at univariable level with either PWV ($p = 0.08$) or AI ($p = 0.44$) in the present study. In contrast, the Anglo-Cardiff Collaborative Trial (ACCT) (McEniery et al. 2005) and Atherosclerosis Risk in Young Adults study (van Trijp et al. 2004) indicated MAP was a determinant of AI. Contrasting findings are possibly due to relatively larger sample size of the latter studies and may also reflect the differential

effects of CKD on prevalence of vascular calcification. Interestingly, when MAP was substituted for systolic blood pressure in the PWV model and entered into the AI model it was retained as a predictor of both vascular indices (appendices XXVI a and XXVI b). Hypertension thus emerged as an independent risk factor for both vascular indices but there is also evidence of a bi-directional relationship with increased arterial stiffness implicated in the pathogenesis of systolic hypertension (Zieman et al. 2005; Tyberg et al. 2008).

6.4.5.5 Relationship between pulse wave velocity and augmentation index

Augmentation index and PWV were not significantly associated in the present study (Spearman's rho = 0.17, p = 0.15), a surprising finding as both indices are proposed as local and composite measures of arterial stiffness respectively. This finding adds to a growing body of literature showing little consensus regarding the relationship between PWV and AI (Tanaka et al. 1998; Yasmin and Brown 1999; Kelly et al. 2001; Lemogoum et al. 2004; Kullo et al. 2005; McEniery et al. 2005; Cheng et al. 2007; Sakurai et al. 2007). It is suggested that the differential effect of aging on these indices in a clinical population of advanced average age is largely responsible for the observed lack of association. Moreover, extensive modelling by Westerhof and Westerhof (2012) demonstrated aortic stiffness increases wave reflection magnitude and AI, but that this increase diminishes with greater stiffness.

In contrast London et al. (1992) found PWV and AI correlated moderately in a mixed cohort of HD patients and controls but no subgroup analysis was undertaken for participants with stage 5 CKD. A larger mortality study involving maintenance HD patients by the same research group reported PWV was an independent predictor of AI, however the coefficient and confidence intervals were not stated (London et al. 2001). Although age demographic was similar, diabetic participants in the cited studies were either far fewer (10%) or absent (London et al. 2001a and London et al. 1992 respectively). This may be an important difference in light of the dissociation between PWV and AI values observed for diabetics. Furthermore, the present study included people with peripheral arterial disease (PAD), which may have resulted in higher AI for a given PWV due altered wave reflections from arterial obstructions or terminal aorta (Safar et al. 2007). Although Yasmin and Brown (1999) reported PWV was a determinant of AI, their findings indicated a clinically meaningful change in the former of 1 m/s was associated with an incremental

change of just 0.4% in AI (Yasmin and Brown 1999). Importantly, this result does not translate to an equivalent level of increased mortality risk.

There is evidence that AI is more sensitive than PWV to volume change among HD patients (Vuurmans et al. 2002; Georgianos et al. 2013). Moreover, studies of healthy males (Kelly et al. 2001) and cardiac patients (Sakurai et al. 2007) have shown similar preferential sensitivity for AI to vasoactive drugs. Despite a similar percentage of treated hypertensive participants (52%) in the study of London et al. (2001a), participants in the current study demonstrated more favourable mean values for vascular outcomes (MAP, PWV, AI were 10.3%, 31% and 21.5% lower respectively). It is suggested participants' antihypertensive regimens were better optimized and this difference may have influenced the AI-PWV relationship.

6.4.6.1 Arterial stiffness and cardiorespiratory fitness

The moderate inverse association ($r = -0.45$, $p < 0.001$) observed between PWV and the ISWT observed here is in agreement with similar findings in the general literature across a wide age range (Vaitkevicius et al. 1993; Tanaka et al. 2000; Boreham et al. 2004; Gando et al. 2010b. The correlation with AI was more modest (Pearson $r = -0.31$, $p = 0.01$) and lower than the moderate correlations reported between AI and cardiopulmonary exercise test (CPET) measured VO_{2max} ($r = 0.41$ to 0.63, $p < 0.001$) of healthy adults (Vaitkevicius et al. 1993; Tanaka et al. 1998).

An important coupling has been proposed between ventricular systolic and aortic function, which is physiologically matched for optimum cardiac efficiency (Chen et al. 1998). Increased arterial stiffness negatively affects cardiac function by increasing aortic impedance to stroke volume from the left ventricle (Shibata et al. 2008) contributing to LVH, and eventually heart failure (London et al. 1990; Nitta et al. 2004). It is suggested that the coupling between aortic stiffness and cardiac function thus mediates in part lower CRF which is highly prevalent in this population. Similarly, increased wave reflections are believed contribute to widening of central pulse pressure resulting in increased myocardial load and reduced coronary perfusion during diastole (London and Pannier 2010). This result may provide some physiological insight as to why CRF is predictive of premature mortality of people with CKD (Sietsema et al. 2004; Gulati et al. 2012).

Aerobic fitness did not emerge as an independent predictor of PWV but this is consistent with a study of healthy sedentary adults of similar age (Vaitkevicius et al.

1993). In contrast observational studies following participants from adolescence to adulthood have reported an independent association between CPET measured CRF and PWV (Ferreira et al. 2003; Boreham et al. 2004). Notably, the result of Ferreira et al. (2003) pertained to peripheral but not central arterial stiffness, which is not predictive of CV mortality in stage 5 CKD (Pannier et al. 2005).

In addition, the ISWT was not retained as an independent predictor of AI while Vaitkevicius et al. (1993) observed CPET measured VO_{2max} was. Although participant age demographic was similar, participants' aerobic capacity in the present study was considerably lower with nearly 90% of ISWT performances in the lowest 25th percentile of age equivalent norm values established by Harrison et al. (2013). Heteroscedasticity of the ISWT data and measurement error associated with employing a proxy measure of fitness are suggested as plausible explanations for the discrepant findings compared to the general literature. Arterial stiffness measures obtained from different devices, which are known to produce significantly different values (Hickson et al. 2009) and different methods of deriving AI values may have also contributed. Notably, although Vaitkevicius et al. (1993) found CRF to be predictive of AI, a 1 MET change in fitness equated to an incremental change of just 1.2% in AI (Vaitkevicius et al. 1993). Pragmatically such a change might not be greater than the measurement variability associated with AI in this study. Crucially a change of 10% in AI is equal to a 48% change in CV mortality risk (London et al. 2001a). In contrast, the study of Boreham et al. (2004) indicated a CRF change of 1 MET equated to a 0.5 m/s change in PWV. This amount of change not only comfortably exceeds measurement variability for this index but also represents a 7% increased risk of CV mortality (London et al. 2001a; Blacher et al. 2003; Verbeke et al. 2011). Illustratively in order for AI to demonstrate a comparable level of CV risk a change of 2.5 METS would be required.

6.4.6.2 Physical activity and arterial stiffness

Physical activity was inversely associated with PWV which is in agreement with cross-sectional and observational studies showing significant associations between indices of central arterial stiffness and PA derived via accelerometry (Sugawara et al. 2006; Kozakova et al. 2007; Aoyagi et al. 2010; Gando et al. 2010b; Jennersjo et al. 2012) and self report (Boreham et al. 2004; van de Laar et al. 2010). Surprisingly PA was not correlated with AI. This result contrasts with the study of Edwards et al. (2012) and may be due in part to a considerably younger age demographic and use

of a different (uniaxial) accelerometer in the cited study. Importantly, habitual PA level was not independently predictive of either index of arterial stiffness in this sample of maintenance HD patients.

This data suggest that arterial stiffness may not be refractory to manipulation of PA behaviour in maintenance HD patients. This is a disturbing result given the prognostic utility of arterial stiffness indices in this population (London et al. 2001; Shoji et al. 2001; Blacher et al. 2003; Verbeke et al. 2011) and that attenuation of PWV is associated with improved survival of people with stage 5 CKD (Guerin et al. 2001). In addition, this finding appears to be at odds with studies reporting reductions in arterial stiffness following PA interventions involving HD patients (Mustata et al. 2004; Toussaint et al. 2008a), healthy postmenopausal women (Moreau et al. 2003; Sugawara et al. 2006), middle-aged and older men (Tanaka et al. 2000). It is possible that this 'negative' finding could reflect the relative homogeneity of PA behaviour (limited inter-individual variation) mediated via thrice weekly HD. It is also possible that variations in PA due to intercurrent illness and fluctuating symptoms commonplace in stage 5 CKD (Nelson-Danquah et al. 2010) may have influenced this relationship.

Two behavioural outliers (appendix XXVII a) may have influenced the results, but subsequent analysis with these participants removed did not alter the models and the association with PA remained non-significant ($p = 0.77$). Accelerometers provide an objective estimate of PA but they do not capture all PA that might be beneficial to health (Troiano et al. 2008). Nevertheless, Kozakova et al. (2007) reported uniaxial PA counts/day were independently predictive of carotid artery stiffness in a large sample of middle-aged adults. Moreover, steps/day, light and moderate PA have been observed to independently attenuate carotid artery stiffness (Sugawara et al. 2006) and aortic PWV (Aoyagi et al. 2010; Gando et al. 2010b) of older adults. Categorised accelerometer variables were not employed in the present study in light of the limitations regarding validity of these outcomes as discussed in chapter 4. However, re-analysis using discrete PA variables rather than a gross measure of general PA may not necessarily yield a different final result due to marked heteroscedasticity of the PA data in the present study. Inspection of the PA versus PWV scatterplot shows most participants at the lower end of the PA spectrum (appendix XXVII b), which was not evident in the studies of Aoyagi et al. (2010) and Sugawara et al. (2006).

6.4.7.1 Application of findings and further research

Despite medical advances epidemiologic observations highlight poor longevity among people receiving maintenance HD therapy, an observation that is more pronounced among younger individuals. These data indicate that although uraemia *per se* does not appear to influence arterial stiffness the longer people remain on HD then they appear to be exposed to a greater risk of accelerated vascular aging. As a risk factor HD vintage is extremely challenging to address in light of the chronic shortage of replacement kidneys available for transplant. This finding underscores the need for further research regarding health interventions to augment current medical management and reduce the impact of HD vintage as a CV risk factor.

Accumulating evidence indicates PA that maintains or improves CRF exerts a beneficial effect directly on the vascular system. However, the most salient finding of this study was that PA and CRF were not independently associated with arterial stiffness indices and thus may not be modifiable via these vectors. Larger cohort studies are recommended to validate these findings. Moreover, appropriately powered randomized control trials which manipulate the PA variable are required to test this hypothesis. In the interim it does raise questions over how PA mediates a beneficial influence on CVD mortality in stage 5 CKD. Pulse wave velocity is a measure of arterial wall structure, which has upstream effects on heart morphology and function (Nichols and O'Rourke 1998; Nitta et al. 2004). However, endothelial function regulates vascular tone and represents an important functional component of large artery stiffness in people with hypertension, diabetes and coronary artery disease (Nigam et al. 2003; Ravikumar et al. 2002; McEniery et al. 2006; Wallace et al. 2007; Bruno et al. 2012). It is possible PA ameliorates CV mortality risk via improved endothelial function in the absence of PWV changes, as observed in elderly hypertensive adults (Westhoff et al. 2007). Future studies investigating arterial health interventions in stage 5 CKD should consider using this index of vascular function as well as arterial stiffness.

Absent associations with important independent CVD risk factors (ie: diabetic status, PA) as well as shortcomings of its formula and underpinning wave theory overshadow the validity of AI in CKD. Moreover, a differential effect of age on AI and PWV (Mitchell et al. 2004; McEniery et al. 2005; Janner et al. 2010) suggests the former may not be as sensitive an index in the CKD population, which is characterised by advanced age. Importantly, while AI is predictive of mortality in

stage 5 CKD (London et al. 2001a), the body of evidence supporting the predictive utility of PWV in stage 5 CKD and the general population is larger and well validated (London et al. 2001a; Blacher et al. 2003; Vlachopoulos et al. 2010; Verbeke et al. 2011). Furthermore, there is evidence that lowering PWV reduces mortality of maintenance HD patients (Guerin et al. 2001). On balance, PWV is recommended as a more suitable arterial stiffness index than AI to assess the impact of interventions aimed at managing CVD risk in the stage 5 CKD population.

Previous studies have documented that interdialytic weight gain is a determinant of 24 hour ambulatory blood pressure of maintenance HD patients (Inrig et al. 2007; Agarwal and Light 2008). Independent association of blood pressure with arterial stiffness is not a novel finding but it does underline the importance of avoiding excessive interdialytic weight gain and optimising anti-hypertensive therapy. It is important to consider however, that lowering heart rate increases AI. Importantly, AI is associated with LVH, and both are predictive of CV mortality in stage 5 CKD (Silberberg et al. 1989; Foley et al. 1995; London et al. 2001a). Heart pacing medications are widely prescribed to manage hypertension in this population (64% in this sample) and are a mainstay of heart failure treatment. Meta-analyses support the benefits of beta-blockers in reducing all cause mortality (Bonet et al. 2000; McAllister et al. 2009) but none have evaluated their effect on risk of sudden cardiac death. Exploration of the distinct haemodynamic influences of different beta-blockers on vascular stiffness/function and CVD mortality in stage 5 CKD is considered an area worthy of further research.

A large percentage of the variance of PWV values remains unexplained. Previous studies have identified a genetic component to arterial stiffness. A polymorphism of the angiotensin II gene is reported to influence large artery stiffness (Benetos et al. 1995). In addition genetic polymorphisms involved with higher elastolytic activity are suggested to influence aortic stiffness (Yasmin et al. 2006). Of particular relevance to stage 5 CKD is the fact that inflammation is associated with genotypes which may negatively affect elastic properties of large arteries (Yasmin et al. 2006). Further research to quantify the genetic influence on arterial stiffness and whether genotypic expression contributing to arterial stiffness may be modified in the HD population is indicated.

Differences are apparent between arterial stiffness values obtained in the present study and those reported in the general literature, as well as the explanatory power

of the models in particular AI. This may be due in part to use of different devices which employ applanation tonometry (SphygmoCor™), mechano-transducers (Complior™), or doppler flow. The Vicorder employed in this study uses oscillometry but is more portable, carries less time burden and is largely operator independent compared to other machines. However, while Vicorder is highly reliable and correlates well with the widely used SphygmoCor™ significant differences in arterial stiffness measures have been observed (Hickson et al. 2009; van Leeuwen-Segarceanu et al. 2010; Kis et al. 2011; Shahin et al. 2013). A correction equation may be employed to improve PWV agreement between these devices but values still remain significantly different (Hickson et al. 2009). Future research should explore methods to enable wider comparison of similar vascular outcomes from different devices and establish the prognostic utility of Vicorder.

6.4.7.2 Study Limitations

Study findings were drawn from cross-sectional data only, therefore it is not possible to draw firm conclusions regarding causality between arterial stiffness and the independent predictors identified here except the risk factor of age. Findings may also have been influenced by participants' medications, however for reasons of safety a prior 12 hour abstention period which may still have been insufficient to nullify all pharmokinetics was not indicated. Measures for participants' clinical biochemistry were obtained within two weeks either side of the vascular measures. Values for these variables fluctuate as can the outcomes themselves. Repeated measures of vascular function analysed as a time-dependent covariate would likely yield a more robust effect estimate for the multivariable models.

The study sample size fulfilled the minimum requirement for multiple regression analysis outlined by Harris (1985) but it was lower than the threshold recommended by Tabachnick and Fidell (2007) of 50 + 8(k) (where k is the number of independent variables). It is possible that independent contribution of metabolic parameters known to affect vascular function such as diabetes was not significant because of the low percentage of affected participants, which in turn may have led to a risk of a type II error.

A strength of this study was the homogeneity of the sample as norm values of arterial stiffness and relative contribution of predictor variables vary according to ethnic background (Chirinos et al. 2011). However, although the study sample comprised just over one third of the HD unit and almost half of those who were

eligible, those who did not participate were significantly older. Therefore while these findings may be generalised to similar UK HD populations caution is urged when applying them to older HD patients as the influence of age is likely to be amplified.

6.5 Conclusion

Arterial stiffness is an important predictor of CV and all cause mortality among people with stage 5 CKD. Apart from age, risk factors for AI and PWV are distinctly different. Additionally, concerns regarding validity of AI and its relatively weaker explanatory model, indicate aortic PWV as the preferred arterial stiffness outcome to monitor interventions to reduce CV risk in the HD population. It is suggested that increased arterial stiffness in stage 5 CKD may not be refractory to PA change. Studies of appropriate rigour are recommended to investigate manipulation of the PA variable and its effect on arterial stiffness. Future research exploring the effect of PA interventions on vascular health in stage 5 CKD should consider assessment of endothelial function to elucidate the relationship between PA, CRF and CV mortality in stage 5 CKD.

What is known about this topic

- Arterial stiffness is an established risk factor for increased CV mortality.
- Stage 5 CKD is characterised by accelerated vascular aging including arterial stiffness.
- Physical activity and CRF are independent predictors of longevity in CKD.
- Physical activity that improves CRF attenuates age attendant arterial stiffening.

What this study adds

- Aortic PWV is indicated as a more appropriate measure of arterial stiffness compared to AI in stage 5 CKD.
- Haemodialysis vintage is an independent risk factor for increased arterial stiffness.
- Increased arterial stiffness may not be influenced by modification of PA behaviour or changes in CRF in stage 5 CKD.

Chapter 7: General Discussion

7.1 Introduction

Life expectancies for people receiving maintenance haemodialysis (HD) for stage 5 chronic kidney disease (CKD) are significantly shortened due to disproportionately high cardiovascular (CV) morbidity and mortality. Physical activity (PA) and physical function (PF) are implicated in health outcomes and the literature is replete with examples of low levels of both in stage 5 CKD. Despite government strategies, health body recommendations and robust epidemiological evidence, counselling practices pertaining to PA and PF in renal care remain inconsistent. An aim of this project was to evaluate elements of contemporary practice relating to PA and PF. This was with a view to providing some recommendations to support healthcare providers and investigators in relation to selection and implementation of assessment methods that also reflect the current shift towards 'person-focused' care. Another aim was to explore whether PA behaviour and fitness may potentially be modifiable risk factors for arterial stiffness, an intermediate CV endpoint.

7.2 Accelerometer minimum wear time recommendations

Accelerometers are increasingly being adopted to characterise PA of maintenance HD patients, but there appears to be a general lack of awareness regarding the need for rigorous data reduction protocols that also ensure ecological validity. Objectives of this study were to determine the minimum accelerometer wear time required to estimate PA and sedentary behaviour with acceptable reliability, and report the impact of wear time criteria on sample retention. The aim was to standardise data reduction methods for accelerometer use in stage 5 CKD.

7.2.1 Study findings

Indices of PA were significantly higher on dialysis days compared to non-dialysis days, which is in agreement with previous research (Majchrzak et al. 2005; Baria et al. 2011; Avesani et al. 2012). Time spent sedentary was significantly greater on dialysis days which is unsurprising given the extended period of enforced sitting required for HD therapy. No significant differences were observed for Actigraph and ActivPAL outcomes across the same condition (ie: dialysis days and non-dialysis days only) and overall, average measure intra-class reliability coefficients for outcome variables normalised to wear time were high (range 0.76 to 0.96). There is debate regarding inclusion of 'weekend' days, but this result suggests such a

requirement is not indicated and is in agreement with studies showing no additional improvement in outcome reliability with weekend day inclusion for adults (McClain et al. 2010; Reid et al. 2013) and children (Penpraze et al. 2006; Rich et al. 2013).

Accelerometer wear time requirements varied according to outcome variable as observed in the general literature (Gretebeck and Montoye 1992; Cook and Lambert 2008; Hart et al. 2011c). Required wear time was lowest for reliable estimates of energy expenditure, steps taken and activity counts/minute (one dialysis day and one non-dialysis day) while one dialysis day and two non-dialysis days were required for indices of PA and sedentary behaviour from both monitors. Overall, it appears that regardless of accelerometer a minimum of three days wear (one dialysis day and two non-dialysis days) will allow sedentary behaviour and most PA indices (normalised to wear time) to be captured with an acceptable reliability level of 0.80. This result is in line with recommendations in the general literature of two to three days accelerometer wear for reliable PA estimates among middle-aged to older adults (Matthews et al. 2002; Rowe et al. 2007; Hart et al. 2011c). The only exception to this recommendation was ActivPAL estimated sit-to-stand transfers/hour, which required six days (three dialysis and three non-dialysis days).

Wear time requirements were generally greater for behaviour indices when they were not normalised to daily wear time. A minimum of four days wear (two dialysis and two non-dialysis days) were required for reliable estimates of total PA minutes/day while the requirement for minutes of sedentary time was even greater at six days (three dialysis and three non-dialysis days). Again, this is line with recommendations in the general literature of five to nine days for the latter (Matthews et al. 2002; Cook and Lambert 2008; Ojiambo et al. 2011; Hart et al. 2011c) and evidence that sedentary time variability is more susceptible to discretionary wear (Masse et al. 2005; Tudor-Locke et al. 2011b).

Computations revealed days with as few as four to six hours accelerometer wear could be included, which contrasts with the widely adopted minimum standard of 10 hours wear to 'rule in' a valid day (Tudor-Locke et al. 2012). However, this standard was derived from research on the effect of wear criteria on sample retention and not measurement reliability (Masse et al. 2005) and may be impractical for low active clinical populations. On balance, a minimum standard of eight hours wear was deemed appropriate due to the amount of time occupied by HD therapy and variation in PA patterns observed around this event (Majchrzak et al. 2005). A

similar daily wear threshold is recommended for low active overweight individuals (Chen et al. 2009; Miller et al. 2013).

Table 7.1 Wear time criteria stringency versus sample size retention.

Wear criteria	1≥ dialysis & 2≥ non-dialysis days, and ≥8 hours/day		1≥ dialysis & 2≥ non-dialysis days, and ≥10 hours/day		7 days and ≥10 hours/day	
Monitor	Actigraph	ActivPAL	Actigraph	ActivPAL	Actigraph	ActivPAL
Sample retained (%)	**90**	**91.4**	**87.1**	**84.3**	**41.4**	**31.4**

7.2.2 Impact of wear time criteria on participant inclusion for analysis.

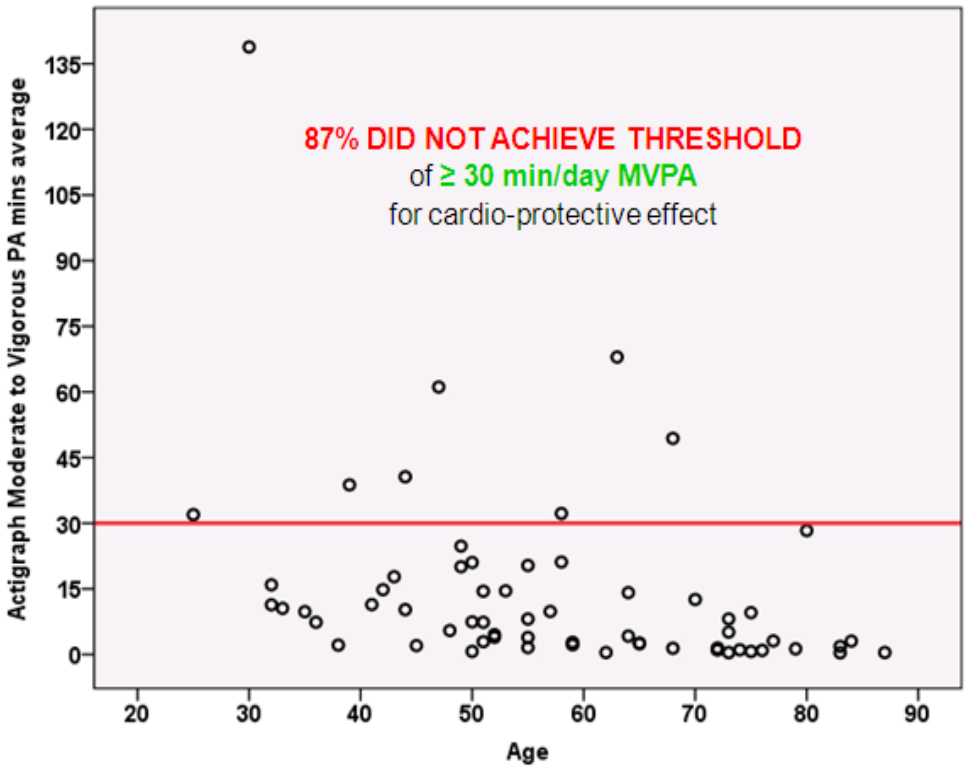
These wear time criteria are proposed with the caveat that they are the minimum requirement only to achieve a clinically acceptable level of reliability. Results indicate seven days of monitoring would endow outcomes with reliability sufficient for measurement at an individual level (Nunally 1978). However, applying such a standard along with the 10 hour/day benchmark would reduce the present sample to less than 50% (table 7.1) of its original size, which is consistent with previous observations (van Coevering et al. 2005; Sirard and Slater 2009; Gemmill 2009). Statistical power would consequently be seriously compromised as well as sample representativeness. Applying the rubric recommended in this study enabled at least 90% of participant PA data to be retained (table 7.1) with a clinically acceptable level of reliability. Application of the 10 hour wear threshold reduced participant numbers by three to six percent but without an appreciable increase in reliability.

Table 7.2 Summary of key findings for chapter three.

What is the minimum wear time for reliable estimates of PA and sedentary behaviour obtained via accelerometry?	Indices of PA and sedentary behaviour are significantly different between dialysis and non-dialysis days but not across the same condition. Regardless of accelerometer used, a minimum of one dialysis day and two non-dialysis days with eight hours wear per day will provide reliable estimates of PA and sedentary behaviour normalised to wear time.
What is the impact of minimum wear criteria on sample size?	Applying these criteria allows 90% of participants to be retained for final analysis.

Figure 7.1 Graph of participants meeting threshold of total PA predictive of mortality and maintaining mobility: Actigraph.

Figure 7.2 Graph of participants meeting consensus PA guidelines associated with a cardio-protective effect: Actigraph.



7.2.3 Recommendations for clinical practice – application of findings

High wear compliance over the 7-day monitoring period (63% and 73% for ActivPAL and Actigraph respectively) supports the feasibility of routine accelerometer use in the clinical, especially as this technology becomes cheaper. Crucially, these data indicate a minimum of three days wear is sufficient to characterise behaviour of maintenance HD patients with acceptable reliability. This is the first time clear recommendations have been proposed for the ActivPAL and for accelerometer use in the HD population. Data reduction guidelines have public health consequence as individuals with monitor wear below criteria required for non-clinical populations may be unnecessarily excluded from analyses. Conversely, insufficient wear time will adversely impact data reliability and the ability to draw appropriate conclusions (Baranowski et al. 2008) and dose-response relationships, which may shape health recommendations (Schatzkin et al. 2009). The value of these recommendations lies in their ability to reconcile the tension between scientific rigour and retention of a sample size that is both sufficient for subsequent analysis and ecologically valid.

The utility of these recommendations is readily demonstrated in figures (7.1) and (7.2). After application of recommended data reduction criteria PA data were stratified according to thresholds associated with mortality risk and mobility in the HD population (Kutsuna et al. 2010; Matsuzawa et al. 2012) and a health enhancing effect for the general population (WHO 2010). The vast majority of participants performed sufficient activity of all intensities to reduce the risk of mortality and deteriorating mobility, but nearly 90% did not achieve the MVPA threshold recommended by consensus PA guidelines. The ability to accurately characterise individuals' PA levels would allow healthcare providers to direct limited resources to those most at risk of poor outcomes. Minimum wear time recommendations were subsequently implemented in the studies exploring the specific contribution of PA to physical function and arterial stiffness of people receiving maintenance HD.

7.3 Concordance of PA assessment methods

Building on the minimum wear recommendations, concordance of similar outcomes from ActivPAL and Actigraph monitors was evaluated with the aim of determining whether they may be used interchangeably for PA surveillance in stage 5 CKD. A substantial amount of data pertaining to PA of HD patients has been obtained via questionnaires. Concordance of self-reported and accelerometer estimated outcomes was also evaluated with the aim of determining whether subjective and

objectively estimated PA data could potentially be pooled.

7.3.1 Study findings -Concordance of Actigraph and ActivPAL

Broad agreement between both accelerometers was found for similar PA outcomes and sedentary time. However, despite strong correlations, statistically significant differences were observed for almost all similar PA outcomes. Actigraph estimated minutes of sedentary time and steps taken were higher and lower respectively compared to ActivPAL estimates, which is in agreement with the general literature (Harrington et al. 2011; Hart et al. 2011a; Hart et al. 2011b; Feito et al. 2012; Ridgers et al. 2012; Matthews et al. 2013; Swartz et al. 2014). Furthermore, an Actigraph data sampling frequency of 15 seconds exacerbated sedentary time disparity closer to bias levels observed by other studies employing the same epoch length (Hart et al. 2011b; Swartz et al. 2014). Crucially, limits of agreement for all similar outcomes were so wide as to prevent their interchangeable use with random (biological) error often increasing proportionally as outcome values increased.

7.3.2 Concordance of subjective and objective estimates of physical activity

Moderate to strong correlations (range 0.55 - 0.71, $p < 0.001$) between similar 7DR and accelerometer outcomes in the present study compare favourably to the modest correlations (average $r = 0.37 \pm 0.25$) reported in the general literature (Prince et al. 2008). However, despite more favourable associations in the present study, large significant differences and wide limits of agreement indicate similar 7DR and accelerometer outcome values (MVPA minutes, EE) cannot be directly compared. The disparity in PA estimates is likely mediated by reporting error associated with self-report (Durante and Ainsworth 1996; Buchowski et al. 1999; Duncan et al. 2001; Loney et al. 2011) and recognised limitations of accelerometry in detecting cycling, upper limb activities, and increased work due to load and gradient (Prince et al. 2008). Additionally, commonly used cutpoints for categorizing Actigraph data appear to be inappropriate for older adults and clinical populations (Miller et al. 2010; Hall et al. 2013), while both accelerometers underestimate EE compared to criterion measures (Leenders et al. 2001; Albinali et al. 2010; Harrington et al. 2011).

7.3.3 Recommendations for clinical practice and research

Concordance studies for these PA assessment tools have previously been undertaken, but this is the first to evaluate level of agreement of all similar outcomes from each method in CKD. Given its prognostic utility there is a strong case for PA

surveillance of clinical populations to be implemented as part of mainstream health assessment. However, investigators and renal healthcare providers need to know which instruments they can invest in for the benefit of their patients and to progress health research. Each of the assessment methods in this study offers different levels of information content with selection dependent on purpose and outcome of interest**.**

7.3.4 Objective versus subjective physical activity assessment

If the requirement is for a broad indication of compliance with PA guidelines on a nomothetic level then self-report methods are an expedient option. However, there is agreement that questionnaires are unsuited to monitoring PA at an individual level (Loney et al. 2011). Questionnaires frequently focus on a relatively narrow range of PA and energy expenditure neglecting lighter intensity ADLs, which appear to maintain mobility (Johansen et al. 2001a; Kutsuna et al. 2010) and confer survival benefits in the HD population (Matsuzawa et al. 2012). Questionnaires such as the 7DR will likely exhibit a floor effect (Tudor-Locke and Myers 2001) in this population, which tends to operate at the lower end of the PA spectrum (Johansen et al. 2007). Furthermore, just three days of accelerometry data are required to characterise PA, which is markedly lower than 14 days for detailed PA logs which require activities to be painstakingly recorded across discrete epochs (Coleman and Epstein 1998; Hart et al. 2011c). Less burdensome 24 hour recall formats still require at least seven to ten days monitoring to achieve similar reliability (Matthews et al. 2001). Moreover, questionnaires are less accurate and reliable for characterising time seated compared to accelerometry (Criniere et al. 2011; Celis-Morales et al. 2012; Wang et al. 2013), which is crucial in light of accumulating evidence linking this behaviour with health outcomes independent of PA level (Owen et al. 2010; Thorp et al. 2011).

A single question regarding exercise frequency is independently predictive of survival in stage 5 CKD, however activity monitors have enabled greater insight into activity patterns of HD patients (Majchrzak et al. 2005; Baria et al. 2011). Moreover, objectively estimated PA is more strongly associated with fatigue symptoms (Gordon et al. 2011), nutritional status (Johansen et al. 2000; Hung et al. 2002; Baria et al. 2011; Cupisti et al. 2011) and risk factors for CV morbidity and mortality (Johansen et al. 2003c; Masuda et al. 2009; Nowicki et al. 2010; Cupisti et al. 2011; Mafra et al. 2011; Avesani et al. 2012). Accelerometry has also demonstrated prognostic utility in the HD population (Kutsuna et al. 2010; Matsuzawa et al. 2012).

Taken together with their superior reliability and evident feasibility, activity monitors are recommended in preference to questionnaires.

7.3.5 Choosing the 'right' accelerometer

Accelerometer choice will depend on the outcome variables of interest. There is agreement from criterion validity studies employing direct observation that the GT3x is less accurate than earlier Actigraph models and ActivPAL for estimating steps taken particularly at slower speeds (Ryan et al. 2006; Harrington et al. 2011; Feito et al. 2012). Similarly, controlled and free-living studies employing direct observation agree ActivPAL has superior accuracy in classifying sedentary time compared to the Actigraph GT3x (Kozey-Keadle et al. 2011; Hart et al. 2011c; Ryde et al. 2012; Lyden et al. 2012). Taken together with findings from the present study, ActivPAL is recommended as the preferred monitor for estimating steps and sedentary time.

Relegating the GT3x from monitoring sedentary behaviour and stepcounts is not a recommendation made lightly given the amount of population-based data and health studies employing Actigraphs. However, the majority of these studies employed earlier Actigraph models, which have greater sensitivity to low frequency movement and superior step count accuracy compared to the GT3x (Rothney et al. 2008; Kozey et al. 2010; Feito et al. 2012). While systematic bias between ActivPAL and GT3x may be ameliorated by manipulation of cutpoint, filter sensitivity or use of triaxial output, there is general agreement level of random error is not (Kozey-Keadle et al. 2011; Lyden et al. 2012; Clemes et al. 2012; Aguilar-Farias et al. 2014). A recent PA intervention study of 67 middle-aged adults found ActivPAL and GT3x sedentary estimates were similarly sensitive to change (Swartz et al. 2014). Thus investigators may still use the GT3x for this metric as long as they are cognisant estimates will be less precise than ActivPAL and that a correction factor cannot be applied to facilitate their interchangeable use.

If the purpose is to monitor or explore the influence of time spent active, this outcome can be obtained from both the Actigraph GT3x and ActivPAL monitors. However, only the Actigraph is presently capable of categorising accelerometer output into different intensities. The limitations of current uniaxial Actigraph cutpoints are apparent from a growing body of research (Staudenmayer et al. 2009; Miller et al. 2010; Albinali et al. 2010; Hall et al. 2013), therefore PA output from this monitor should be reported as activity counts per minute. Although this outcome does not readily translate to current PA guidelines for a health enhancing effect (WHO 2010)

it nevertheless provides a gross, if dimensionless measure of overall activity volume and intensity. Although ActivPAL also records activity counts this outcome is not part of its formal output and requires more technical expertise to extract and process.

Dual use of Actigraph and ActivPAL could provide a more rounded assessment of an individual's activity behaviour in a similar manner to the multiple-sensor Intelligent Device for Energy Expenditure and Activity (IDEEA; MiniSun, Fresno, CA, USA). However, despite promising precision of the latter device (Zhang et al. 2004; Grant et al. 2006) Arvidsson et al. (2009) concluded a single accelerometer was more feasible for use in free-living conditions. Similarly, lower overall compliance for tandem Actigraph and ActivPAL wear in the present study together with extra data processing and cost burden indicate their simultaneous use is not a feasible option.

7.3.6 Monitoring energy expenditure

Choice of assessment method is more flexible for energy expenditure (EE), which is commonly employed for nutrition studies in stage 5 CKD (Cupisti et al. 2011; Baria et al. 2011; Mafra et al. 2011; Avesani et al. 2012). Although, broad agreement was observed for 7DR and accelerometer estimates of EE. there is overwhelming evidence that criterion validity of all instruments for this outcome is poor (Bonnefoy et al. 2001; Leenders et al. 2001; Mahabir et al. 2006; Harrington et al. 2011; Albinali et al. 2010). Inherent limitations of generalising EE estimates derived from the Compendium of Physical Activities (Ainsworth 2011) and assuming the same resting metabolic rate for all individuals have previously been highlighted (Kozey et al. 2010; Hall et al. 2013). While none of these instruments may provide an accurate proxy EE measure they may still serve a useful role in ranking participants.

Table 7.3 Summary of key findings for chapter four.

W**hat is the level of agreement between subjective and objectively estimated PA outcomes in stage 5 CKD?**	Moderate to strong correlations are observed between similar subjective and objective PA outcomes but large significant differences and wide limits of agreement indicate objective and subjective PA outcomes values cannot be directly compared or pooled.
What is the level of agreement between similar outcomes obtained via Actigraph GT3x and ActivPAL accelerometers?	Similar outcomes from ActivPAL and Actigraph accelerometers correlate strongly but level of agreement analysis indicates they may not be used interchangeably. ActivPAL will likely provide more accurate estimates of steps taken and time spent seated.

7.3.7 Physical activity monitoring recommendations and 'big data'

This is the first time recommendations have been made regarding standardisation of PA assessment for people with stage 5 CKD. Not only are they intended to support investigators and healthcare providers with instrument selection but they should also help ensure integrity of PA data obtained. Outcome measure heterogeneity and quality assurance of data are increasingly important technical challenges faced by investigators attempting meaningful synthesis of PA data. These recommendations are timely in light of the inevitable application of 'big data' to health research (Raghupathi and Raghupathi 2014). Standardisation of PA assessment methods will better facilitate pooling of disparate/heterogeneous datasets to create an observational evidence base to answer research questions and potentially guide clinical practice and health policies.

7.3.8 Routine monitoring of physical activity and sedentary behaviour

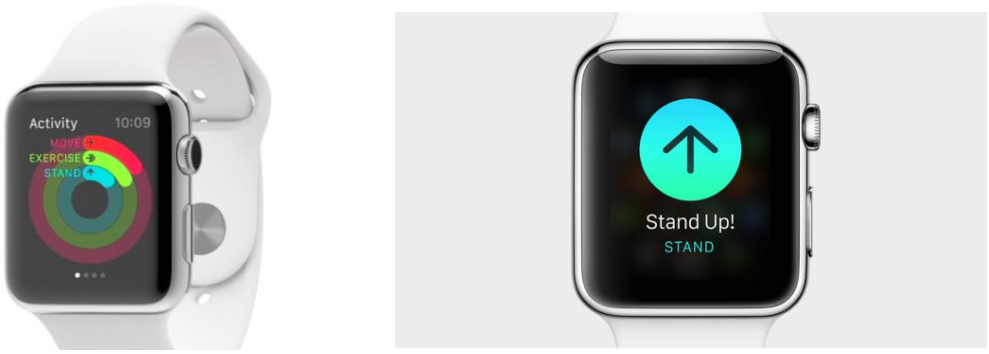
An important issue facing healthcare providers is how PA monitoring may be implemented with minimal additional burden on limited resources, and personnel? Pedometers are a cheap and expedient option but are prone to underestimating steps taken especially in older adults with slower gait (Feito et al. 2012), lessening their suitability for the HD population. Piezo-electric accelerometers and gyroscopes, which were once technology only found in expensive research accelerometers are *de rigueur* in the latest generation of smart phones. In addition there has been a proliferation of PA promoting phone apps (Middelweerd et al. 2014) and bracelet/watch monitors capable of recording numerous physiological indices as well as PA, which can be synchronised to smartphones.

Self-monitoring of PA using emerging technologies now available to consumers is an option that is congruent with Scottish Government health policy of encouraging individuals to become more involved in managing their own health and healthcare (Physical Activity Taskforce 2003). Importantly, ethernet connected smart phone apps offer ecological momentary assessment (EMA) making it feasible for the user to benefit from tailored and timely feedback based on their location (Middelweerd et al. 2014). A North American study documenting an increase in mobile media (non voice) use from 24 minutes to almost two and a half hours between 2010 and 2013 (eMarketer 2013) indicates the potential for PA monitoring and health promotion.

The Apple Watch (figure 7.3) is the latest example of smart communication technology featuring PA monitoring as a standard function. Notably the Watch

incorporates EMA and behaviour change techniques to promote PA as part of its design and function thereby driving repeat usage ('stickiness') and increasing awareness of health behaviours. A novel function of the Watch is its haptic feedback and visual cues prompting the wearer to break up extended periods of sitting. Accumulating evidence indicates the greatest health benefits may be attained simply by a shift from being sedentary (Chief Medical Officers 2011). Consequently, this simple function for monitoring and reducing sitting time may be the most salient application of a device like the Watch in stage 5 CKD. With the exception of the Apple Watch, smart technology PA 'wearables' are often less than one quarter the cost of research grade accelerometers used in the present study (appendix XXVIII).

Figure 7.3 Apple watch.



(Apple 2015)

7.3.9 Research considerations for wear time and PA concordance studies

A strength of the accelerometer wear time study is that actual wear time for each monitor was accurately triangulated (general methods 2.5.4). Limitations of the sample size with respect to Spearman Brown Prophecy calculations were apparent when wear time thresholds to define a valid day increased above eight hours. This tended to affect ActivPAL calculations more than Actigraph due to lower wear compliance and higher malfunction rate observed with the former. Consequently, recommended wear time for total PA and sedentary time estimated via ActivPAL is based on the assumption that reliability would be higher with a larger sample size as observed for Actigraph reliability coefficients.

Reliability of categorised PA and sedentary behaviour outcomes obtained via the Actigraph were derived using the uniaxial cutpoints of Freedson et al. (1998) and Evenson et al. (2008) respectively. Wear time requirements may vary according to alternative cutpoints and prediction equations proposed for uniaxial (Swartz et al.

2000; Hendelman et al. 2000; Crouter et al. 2006; Crouter et al. 2010; Kozey-Keadle et al. 2011) and triaxial Actigraph output (Sasaki et al. 2011; Santos-Lozano et al. 2013; Aguilar-Farías et al. 2014).

The sample size available to evaluate accelerometer outcome agreement was approximately half that originally recruited due to variable adherence in wearing both monitors simultaneously for the prescribed period and device malfunctions. Although sample size was relatively modest the number of participants included was above the threshold of 32 recommended by Liao (2010) for agreement analysis. A more pronounced gender bias was evident in the reduced sample. It is unclear how this may have influenced the results as participant numbers did not permit meaningful gender specific analysis and is an area that merits consideration in future concordance studies. A strength of this study was that monitor wear times were synchronised to ensure that subsequent analyses were undertaken on accelerometer estimated outcomes over the same epoch. This is important, as few ActivPAL and Actigraph concordance studies have explicitly stated this was done, and those that have observe lower estimation discrepancies between the devices.

A criterion measure was not employed in the PA concordance study, therefore definitive statements regarding precision of any of the measures evaluated have been avoided. Gold standard methods such as doubly labelled water, indirect calorimetry and direct observation are recognised criterion measures for proxy estimates of energy expenditure, PA categorisation, steps taken and sedentary time respectively. However, criterion measures are arguably less feasible for PA research in clinical populations. Consequently, recommendations regarding assessment methods were formulated based on observations from the present study, published criterion validity studies, and characteristics of the HD population.

Consensus cutpoints for categorising PA and sedentary behaviour, and calculating EE from triaxial output of the Actigraph GT3x were not available at the time of analysis. Observed disparities between Actigraph and similar outcomes from the 7DR and ActivPAL appear to reflect in part limitations of uniaxial cutpoints for PA and sedentary behaviour originally calibrated in samples of young, healthy adults Freedson et al. (1998) and children (Evenson et al. 2008).

Table 7.5 Summary of research considerations arising from chapters 3 and 4.

- Modest sample size for wear time reliability and concordance analyses increasing observed outcome variability.
- Actigraph triaxial output unable to be categorised for concordance evaluation with ActivPAL.
- Limitations of Freedson et al. (1998) and Evenson et al. (2008) uniaxial cutpoints for categorising PA and sedentary behaviour from Actigraph data.
- Gold standard measurement of similar PA and sedentary behaviour indices not feasible in free-living clinical population.

7.3.10 Recommendations for future research – accelerometer wear time

The three day minimum wear period recommended for these monitors to achieve acceptable reliability may potentially shape study design by shortened monitoring protocols to minimise participant burden and expedite data collection. However, potential bias of purposive sampling from just three days wear should be examined before investigators adopt this approach. Imputation methods for missing or partial accelerometer data developed by Catellier et al. (2005) could potentially be applied in CKD5 PA studies. Although an attractive technique there are recognised limitations regarding how to categorise 'missingness' of absent data and it is recommended that bias of this approach should be examined where possible before it is implemented. Given the smaller participant sample of ActivPAL data available for required wear time calculations it is suggested that recommended wear criteria for this monitor should be verified in a larger cohort of HD patients.

Wear recommendations made here are for research grade accelerometers only and may differ for wearable monitors currently available to consumers and smartphone derived PA outcomes. It is conceivable the latter devices, which appear to have comparable validity to research grade monitors (Lee 2013; Storm et al. 2015) may be used as a more feasible PA surveillance method in stage 5 CKD. If consumer-bought monitors are to be adopted then similar reliability studies should be undertaken to establish minimum wear recommendations for these devices in the HD population.

7.3.11 Recommendations for future research – physical activity assessment

An advantage of accelerometers is that estimates of PA and sedentary behaviour are not influenced by recall difficulties or reporting bias associated with

questionnaires. However limitations of categorised uniaxial Actigraph GT3x output is evident from studies in laboratory (Staudenmeyer et al. 2009; Albinali et al. 2010; Miller et al. 2010; Hall et al. 2013) and free-living conditions (Leenders et al. 2001; Crouter et al. 2013). Moreover categorised triaxial output does not appear to deliver anticipated greater precision in estimating PA (Vanhelst et al. 2012; Hislop et al. 2012) and sedentary behaviour (Aguilar-Farías et al. 2014), particularly in older adults (Santos-Lozano et al. 2013). Crucially, most accelerometer cutpoints and prediction equations rely on single linear models that assume a static parametric relationship between body accelerations and greater physiological cost of diverse activities.

Improved precision of Actigraph EE estimates (15% to 60%) has been reported for artificial neural networks (ANN) employing a more flexible model of activity type detection by drawing on information density of accelerometer signals (Staudenmayer et al. 2009; Albinali et al. 2010; Trost et al. 2012). If Actigraph GT3x triaxial output is to be categorised into meaningful behavioural outcomes for people with CKD then validity of ANN processed data should be evaluated. Research evaluating the potential benefits of processing of raw output to overcome reductions in sensitivity induced by proprietary band pass filtering (Chen et al. 2012) is also suggested. Concordance of similar outcomes between the GT3x and other monitoring methods should then be revisited.

ActivPAL may potentially be employed to monitor activity behaviours and categorise PA intensity as the calibration study of Dowd et al. (2012) demonstrates. Furthermore, gyroscope and accelerometry data obtained from the ActivPAL could be integrated to improve accuracy of PA estimates as indicated by small-scale studies evaluating smartphones (Wu et al. 2012; Lee 2013; Shoaib et al. 2014). Calibration studies exploring integration of ActivPAL gyroscope and accelerometer data are warranted to evaluate the possibility of one monitor for estimating behaviours as well as categorising PA.

It is forecast that by 2016 there will be one billion smartphone owners worldwide (ABIresearch 2015). An advantage of ‘ethernet’ connectivity of low cost consumer-bought wearables is that regular health based PA monitoring should be more feasible. This has potentially huge benefits for ‘person focused’ care, which implies health care that is continuous, based on greater knowledge of the individual and not confined to medical visits (Starfield 2011). Feasibility studies of smartphone

connected existing and emerging 'wearables' such as 'smart shoes' (Edgar et al. 2012; Dannicker et al. 2013) for routine PA surveillance in stage 5 CKD are urged.

Prognostic utility of objectively estimated PA for mobility and all cause mortality has thus far only been demonstrated in two single centre studies involving no more than 202 Japanese maintenance HD patients (Kutsuna et al. 2010; Matsuzawa et al. 2012). If adoption of objective PA monitoring is to be encouraged as part of routine healthcare then multi-centre studies examining prognostic utility of accelerometer outcomes are crucial. Future studies should not only delineate the dose-response of different levels of PA intensity on health outcomes but also the effect of bout length.

In light of increasing use of motion sensors for PA surveillance and promotion and overwhelming evidence of their poor concordance with questionnaires, existing PA guidelines developed from self-report data will likely require recalibration. Guidelines on sedentary behaviour published recently by Buckley et al. (2015) recommend accumulating two hours of standing or light activity per day with progression to a total of four hours. However, these recommendations are targeted at asymptomatic individuals in predominantly desk-based occupations. Given the unique characteristics of the HD population, research examining the prognostic utility of objectively estimated time seated, breaks in sitting and changes in these sedentary behaviour metrics is strongly urged to develop HD population specific guidelines.

Findings from the previous studies resulted in the selection and implementation of the Actigraph GT3x monitor and data reduction criteria in subsequent studies exploring the relative contribution of PA to physical function and arterial stiffness. The Actigraph GT3X was selected as its activity count output provides an indication of PA intensity as well as volume. Moreover the Actigraph had no days lost to device malfunction whereas the ActivPAL had 35 lost data days. In addition Actigraph monitors have been employed in previous stage 5 CKD research (Greenwood et al. 2012), as well as large population based studies (Matthews et al. 2008) allowing greater contextualisation.

7.4 Physical function and stage 5 CKD

Routine monitoring of PF has been recommended as part of health management in this population (NKF 2005) but there is little guidance as to how this should be achieved. There is a pressing need to identify the most useful PF outcomes to support renal healthcare providers in nephrology implement KDOQI recommendations. This study explored potential clinical and demographic correlates

of functional capacity across a wider spectrum of physical performance tests, with applicability to common daily activities than has previously been undertaken.

7.4.1 Study findings

A high proportion of participants exhibited impaired physical performance, similar in magnitude to findings from larger cohorts of maintenance HD patients (Stenvinkel et al. 2002; Nonoyama et al. 2010; Silva et al. 2011; Greenwood et al. 2012). Functional status indicated by the physical component summary (PCS) score of the KDQOL-SF was 7% lower than the average reported for the multi-continent Dialysis Outcomes and Practice Patterns Study (DOPPS) despite similar participant demographics (Mapes et al. 2003). Illustratively, test performances indicated at least 40% of participants might be unable to cross a road safely and were generally lower than those for individuals 10 to 20 years more senior. Moreover functional capacity and self-reported functional status outcomes for at least 83% of participants were in the lowest 25th percentile for age equivalent norms. Worryingly, PCS scores indicated three quarters of the sample were at or below a threshold associated with 50% higher mortality risk for HD patients over six years (Feroze et al. 2011).

Condition specific variables (dialysis adequacy, anaemia status) *per se* did not influence PF in this sample of HD patients. Instead factors typically associated with other long-term conditions (age; multi-morbidity; polypharmacy; reduced muscle mass; nutritional status; inflammation) were correlated and contributed one quarter to a half of the explained variance. Number of correlated variables increased concomitantly with greater neuromuscular complexity and integrated physiological demand of the task. Notably, habitual PA made the greatest relative contribution to functional capacity (shuttle walk, sit-to-stand five) and attenuated or nullified the contribution of other variables (ie: number of medications, BMI, age). This result extends the findings of Johansen et al. (2001a) and Kutsuna et al. (2010) who observed habitual PA was a determinant of self-selected gait speed. This is important, as not only should PF outcomes have clinical utility but if they are to work in tandem with PA promotion strategies then ideally they should also be sensitive to behavioural change.

Table 7.6 Summary of key findings for chapter five.

What are the correlates of physical performance measures of function in stage 5 CKD?	Number of correlates increased with complexity of task. Factors typically associated with a long-term condition were correlated with physical function.
What are the correlates self-reported measures of function in stage 5 CKD?	Multivariable models explained a quarter to a half of the variance in physical performance but less than 25% of the variance in self-reported functional status.
What is the relative contribution of physical activity to physical performance and self-reported measures of physical function in stage 5 CKD	Correlations with condition specific variables (anaemia status and dialysis adequacy) were notably absent. Habitual PA was independently associated with distance walked during the shuttle walk test and sit-to-stand five test time and made the largest relative contribution to the variance explained for each. PA attenuated or nullified the effect of other potential predictor variables notably age. PA was independently associated with PCS from KDQOL only but a significant main effect for gender was observed.

7.4.2 Practical application of monitoring physical function – frailty

Central to the concept of 'person-focused care' is recognition and appropriate care of the individual's problems which are "often *not* diagnoses but rather symptoms and signs" (Starfield 2011, p. 65). A growing body of evidence underlines the importance of implementing routine monitoring of physical function as a 'sixth vital sign' in addition to traditionally monitored physiological indices (blood pressure, pulse and respiration rate, blood oxygen level, temperature) (Bierman 2001; Fritz and Lusardi 2009). There is growing recognition of the importance of undiagnosed frailty on health outcomes of HD patients (Painter et al. 2013). Application of accepted frailty criteria using the outcomes employed here revealed one quarter of prevalent HD patients in this study were classified as frail, which is in agreement with previous research (Painter and Kuskowski 2013). This is important as adjusted mortality risk of people who present as frail at initiation of HD is more than doubled at one year (Johansen et al. 2007) and almost threefold higher for individuals who become frail over three years (McAdams-Demarco et al. 2013). Early identification of frailty facilitated by PF monitoring may thus play a crucial role in early identification of

individuals at risk of poor outcomes. Timely interventions could then be targeted to ameliorate functional decline, and reduce the risk of hospitalisations and mortality..

7.4.3 Recommendations for clinical practice

Overall, these data are supportive of KDOQI recommendation for incorporation of physical function outcomes as a standard part of clinical service. Quarterly and six-monthly monitoring of physical function are recommended by Painter and Marcus (2013) and the KDOQI (NKF 2005) respectively. Whilst, the former is preferable the latter seems an appropriate minimum standard given a (10 point) decrease in PCS score over six months is predictive of 25% higher mortality risk at one year among HD patients (Knight et al. 2003). Physical function assessment is recommended as part of care during hospital inpatient stay due to intercurrent illness.

7.4.4 Physical performance tests versus self-reported functional status

Functional status questionnaires afford a unique 'person centred' perspective of an individual's functional status, and there is ample evidence of their prognostic utility in stage 5 CKD (table 1.14, chapter 1). However, less than 25% of the variance in PCS and DASI scores was explained by demographic and clinical variables. This result is consistent with literature indicating functional status is more heavily influenced by psychosocial factors compared to physical performance (Carmichael et al. 2000; Lord et al. 2002; Bean et al. 2011). Notably, habitual PA made a limited contribution to functional status indicated by the PCS with a significant main effect for gender, suggesting this outcome may only be sensitive to behaviour change in males.

Other recognised shortcomings of functional status questionnaires include lower reliability compared to physical performance tests (Davey et al. 2003; Overend et al. 2010), response bias (Sjöström et al. 1999) and appropriateness for people with cognitive deficits (Guralnik et al. 1989). Questionnaire scores are also influenced by temporal variation (Nelson-Danquah et al. 2010) and method of administration (Weingberger et al. 1996; Lyons et al. 1999). Moreover, using functional status instead of physical performance to determine frailty has been shown to triple the percentage of HD patients with this diagnosis (Painter and Kuskowski 2013). The high participation rate observed in the present study (95 to 100% of consented participants) with no adverse events indicates physical performance testing is a feasible means of monitoring functional ability of people with stage 5 CKD. On balance, physical performance tests are recommended as the preferred option over

functional status in stage 5 CKD. If questionnaires are to be employed they should not be used in isolation but in tandem with the former.

7.4.5 Which physical performance test/s?

As with PA assessment, selection of physical performance test/s is determined by intended purpose, outcome, and whether it can be operationalised as part of routine care (Koufaki and Mercer 2009). The STS5 and TUAG are predictive of balance impairment (Whitney et al. 2005), bone fractures (Jamal et al. 2006), and falls (Shumway-Cook et al. 2000; Cook and Jassal et al. 2008; Tiedeman et al. 2008; Buatois et al. 2010; Wrisley and Kumar 2010) in the CKD and general population. The importance of their prognostic utility cannot be overstated given older adults in this population are beset with a falls incidence over three times higher than asymptomatic individuals (12.7% versus 4% respectively) (Desmet et al. 2004 and Hestekin et al. 2013 respectively). Additionally, slow TUAG times are incrementally predictive of premature mortality in CKD (Roshanraven et al. 2013). Neither test elicits a maximal cardiorespiratory response and they can be administered in under two minutes on a dialysis day visit. The TUAG and STS5 are recommended as the minimum standard for assessing physical function in stage 5 CKD.

These data suggest the ISWT may be the more sensitive outcome for monitoring behavioural change and PA interventions. Moreover, it measures a wide level of ability making it less susceptible to ceiling effects (Painter and Marcus 2013) and arguably more suited to stratifying CV risk in younger individuals who experience the greatest relative reductions in life expectancy (SRRR 2011). However, due to fluctuations in fluid status this symptom-limited maximal walking test may only be performed safely on an interdialytic day. Attendance outside scheduled HD sessions could present a significant barrier to compliance given the high ‘did not attend’ rate observed during this project (39 of 112 scheduled appointments). Routine adoption of the ISWT in the HD population for younger individuals in particular is likely best achieved by incorporating this test into a non-dialysis day medical appointment.

Physical activity was not independently associated with handgrip strength in the present study, however this test has prognostic utility with respect to nutritional status, CV and all-cause mortality (Al Snih et al. 2002; Stenvinkel et al. 2002; Qureshi et al. 2002; Rantanen et al. 2003; Wang et al. 2005; Dong et al. 2008) and is an easily attained core component of Fried’s frailty phenotype (Fried et al. 2001). Given the high prevalence of frailty in this population and its impact on health

outcomes it would seem prudent to deploy this expedient test for frailty screening if an individual is unable to undertake the STS5 or TUAG tests.

One or all of these tests may be combined to provide a more comprehensive assessment to stratify for risk of CVD, falls and frailty. The short physical performance battery (SPPB) is a multiple test instrument with prognostic utility in the elderly (Guralnik et al. 1994) that has been employed in CKD (Hall et al. 2012; Abreo et al. 2014). A potential limitation of the SPPB is that it was designed primarily to assess lower limb function of older adults. Although stage 5 CKD is characterised by high average age, this demographic is bi-modally distributed (SRRR 2013) which may result in ceiling effects for the large proportion of younger people. Moreover the SPPB subtask with greatest prognostic value is the STS5 suggesting the balance and walk items may be less important in routine monitoring (Cesari et al. 2008).

7.4.6 Future research recommendations

The influence of polypharmacy on physical performance was highlighted in this study likely due its influence on balance impairment (Agostini et al. 2004). However, some blood pressure and cholesterol medications commonly prescribed in this population are known to have differential myopathic (Tomaszewski et al. 2011) and myo-protective effects (Onder et al. 2006) respectively. Lean muscle mass is linearly related to muscle strength (Overend et al. 1992; Newman et al. 2003; Rolland et al. 2008), which is a determinant of PF in stage 5 CKD (Diesel et al. 1993). The effect of ACE inhibitors and statins on phenotypic expression of genes associated with skeletal muscle response to PA is considered an area worthy of further research.

Physical performance tests selected for this study are predictive of health outcomes but additional data are required to support investment and reliance on the evidence provided by some of these tests for the benefit of people with stage 5 CKD. Handgrip strength is reportedly prognostic of health outcomes, but further research is required to delineate clinically important thresholds pertaining to mortality and malnourishment in CKD. Cardiorespiratory fitness above five METs obtained via cardiopulmonary exercise test (CPET) confers improved survival among maintenance HD patients (Sietsema et al. 2004) and across the CKD trajectory (Gulati et al. 2012). Although the Incremental Shuttle Walk Test (ISWT) is proposed as a proxy measure of CRF it does not possess equivalent predictive ability to CPET for people with CHF (Pulz et al. 2008). Further evaluation of the prognostic utility of the ISWT with respect to health outcomes in CKD is warranted.

A dearth of studies support the prognostic utility of functional status outcomes in stage 5 CKD. However, habitual PA had little or no influence on the KDQOL-SF PCS and DASI scores respectively in this sample of HD patients. The Human Activity profile (HAP) (Fix and Daughton 1988) is more strongly associated with PA compared to SF-36 PCS scores of maintenance HD patients (Johansen et al. 2001b). Moreover, it was independently predictive of mortality risk in the recent Comprehensive Dialysis Study (Johansen et al. 2013). The HAP also has superior sensitivity in detecting changing medical status in people who have undergone allogeneic hematopoietic stem cell transplantation (Herzberg et al. 2010). It is speculated the HAP may be more likely to fulfil criteria of sensitivity to physiological and behavioural change and should be explored.

These data indicate habitual PA attenuates declining physical function, which is consistent with numerous studies reporting significant improvements in functional outcomes following structured PA interventions (Parsons and King-van Vlack 2009). However, it is not known whether subsequent improvements in PF translate to lower mortality and morbidity in stage 5 CKD. Research in this area is warranted but may prove challenging in a randomised controlled study of adequate length due to ethical considerations. Future health intervention studies with intermediate endpoints should also explore interactions with changes in physical function.

7.5 Arterial stiffness and stage 5 CKD

Cardiovascular disease (CVD) is the main threat to survival in stage 5 CKD mediated largely by increased central arterial stiffness, a strong predictor of CV mortality in this population (London et al. 2011; Verbeke et al. 2011). Physical activity and cardiorespiratory fitness (CRF) are implicated in CV and all cause mortality in stage 5 CKD but it is unclear whether they are potentially modifiable risk factors for arterial stiffness. .The objective of this study was to explore clinical and behavioural correlates of arterial stiffness in stage 5 CKD.

7.5.1 Study findings

Age and blood pressure were the principal drivers of aortic pulse wave velocity (PWV), which is in agreement with findings from large (Shoji et al. 2001; Blacher et al. 2003; Townsend et al. 2010) and small cohorts of maintenance HD patients, and people with less severe CKD (Temmar et al. 2010) and asymptomatic adults (Yasmin et al. 2006; Achimastos et al. 2010). This result is consistent with putative mechanisms of age-attendant changes in arterial extracellular matrix, as well as

central pressure-mediated wall hypertrophy (Laurant et al. 2005) and loading of stiffer collagen fibres (Bank et al. 1996). Factors pertaining to fluid dynamics (height, heart rate, haemoglobin level, BMI) explained more of the variance in AI, which is in line with previous studies of HD patients (London et al. 1992; London et al. 2001a).

Stage 5 CKD is independently associated with arterial stiffness (London et al. 1992) but this is the first time HD vintage has been identified as a predictor. Notably, less than six years of HD treatment exposure equated to an incremental increase of 1 m/s and thus 15% higher mortality risk (Blacher et al. 2003) compared to a threshold of 14.3 years of chronological age increase. Importantly, this result corroborates closely with findings from a demographically similar cohort of 80 prevalent HD patients observing an average 0.6 ± 0.2 m/s increase in Doppler measured aortic PWV over three years (Avramovski et al. 2013). It is also consistent with studies showing increased severity and prevalence of vascular calcification (Sigrist et al. 2007) and left ventricular hypertrophy following initiation of HD (Foley et al. 2010).

Hypertrophic effects of chronically elevated blood pressure on arterial walls are well documented, but uraemia is also characterised by endocrine and metabolic dysregulation. Bone demineralisation mediates higher serum levels of phosphate, which has a direct calcifying effect on the tunica media (Jono et al. 2000). Dialysis-induced physical inactivity and muscle atrophy (Johansen et al. 2003a) likely precipitates a cascade of insulin resistance and an increase of advanced glycation end products (AGEs). As well as having direct effects on arterial wall architecture AGEs generate reactive oxygen species quenching endogenous nitric oxide (a vasorelaxant) and provoke an immunological response (Zhang 2008). Inflammatory cytokines are implicated in vascular smooth muscle proliferation (Park and Lakatta 2012), reduction of endogenous calcification inhibitors (Memoli et al. 2007) and endothelial dysfunction (Gunnett et al. 2005). In addition, dialysis may remove some endogenous calcification inhibitors (Lomashvili et al. 2005). It is speculated some or all of these factors conspire in concert to make uraemia especially pernicious to the structural and functional components of arteries.

Notably, PA and a surrogate measure of CRF (the ISWT) were not retained in the multivariable models as additional predictors. Conversely, several studies report higher levels of PA independently predict lower carotid artery (Sugawara et al. 2006) and aortic stiffness (Aoyagi et al. 2010; Gando et al. 2010b) of older adults. Higher CRF independently attenuates central arterial stiffness of endurance trained seniors

(Vaitkevicius et al. 1993) and individuals followed from adolescence to adulthood (Ferreira et al. 2003; Boreham et al. 2004). Use of the ISWT in the present study instead of CPET derived VO_{2peak} may partially explain the contrasting findings. In addition, heteroscedasticity of the ISWT and PA data and homogeneity of participant behaviour resulting in lower variability is speculated to have contributed

A worrying implication is that central arterial stiffness, which is a strong predictor of mortality may not be modifiable with behaviour change at this stage of the CKD trajectory and that arteriosclerosis is irreversible. It is possible that mortality risk may only be ameliorated in HD patients who show a reduction in BP and PWV following aggressive pharmacological intervention (Guerin et al. 2001). Interestingly, a number of clinical markers believed to influence arterial calcification and stiffness in stage 5 CKD were either not correlated (c-reactive protein, serum calcium, parathyroid hormone) or paradoxically associated (serum phosphate, serum creatinine). It is speculated this may be because of the high prevalence of advanced calcification of the tunica media in the HD population (Sigrist et al. 2007).

If habitual PA is the most important modifiable predictor of CRF and both are prognostic of outcomes, the question is by what vector do they confer improved survival in stage 5 CKD? Arterial stiffness is reported to have a large heritable component with genes responsible for arterial matrix proteins, endothelial function, renin-angiotensin-aldosterone axis, endogenous calcification inhibitors and inflammation implicated (Lacolley et al. 2009). An *in vivo* study of chronic aerobic exercise in a murine model found cardiac endothelial cell gene expression was up regulated while IL-6 gene expression was down regulated (Matsumoto et al. 2012). Notably higher serum levels of IL-6 levels are know to down-regulate Fetuin-A a potent systemic calcification inhibitor (Memoli et al. 2007). It is speculated that higher PA may mediate lower CV risk in CKD5 by modifying phenotypic expression of genetic determinants of arterial stiffness. Physical activity may be more closely related to biomarkers of putative arterial stiffness mechanisms as many of these factors have their genesis in physical inactivity. A three week pilot study of aerobic exercise involving elderly CHF patients found serum levels of matrix metalloproteases implicated in deleterious vascular remodelling were reduced while serum levels of endothelial progenitor cells increased (Gatta et al. 2010).

7.5.2 Indices of central arterial stiffness are not related in stage 5 CKD.

The finding that PWV and AI were not related in this study adds to a growing body of conflicting literature regarding the relationship between these indices (Tanaka et al. 1998; Yasmin and Brown 1999; Kelly et al. 2001; Lemogoum et al. 2004; Kullo et al. 2005; McEniery et al. 2005; Cheng et al. 2007; Sakurai et al. 2007). Changes in AI are dependent on many factors and not just the amplitude of the reflected pressure wave and augmentation pressure, suggesting a mathematical flaw in the formula for this index (Cheng et al. 2007). Although aortic stiffness increases wave reflection magnitude and AI, this effect diminishes with greater PWV (Westerhof and Westerhof 2012). Moreover, invasive pulse wave analysis studies employing the reservoir-wave approach indicate substantial non-wave related effects of aortic volume on aortic pressure, and that wave reflection explains just 5.8% of AI variance (Tyberg et al. 2008; Tyberg et al. 2009). Thus, observed lack of association between AI and PWV is likely due to the way AI is calculated and its underpinning wave theory, which does not take into account the cushioning effect of the aorta.

Table 7.7 Summary of key findings for chapter six.

What are the correlates of arterial stiffness in stage 5 CKD?	Age and blood pressure independently predicted indices of arterial stiffness and were the principal determinants of aortic PWV. HD vintage also predictive of PWV in a model that explained 60% of the variance in this index. Heart rate, height and haemoglobin level make a greater relative contribution to augmentation index.
What is the relative contribution of PA to indices of arterial stiffness in stage 5 CKD?	Habitual physical activity and a physical performance measure of cardio respiratory fitness correlated with arterial stiffness indices but were not retained as independent predictors when added to the multivariable models. Augmentation index and PWV are not related in this sample of maintenance HD patients.

7.5.3 Recommendation for clinical practice – Which arterial stiffness index?

There is general agreement PWV and AI demonstrate divergent trends with advancing age (Mitchell et al. 2004; McEniery et al. 2005; Janner et al. 2010) and dissociative findings for diabetics (Westerbacka et al. 2000; Ravikumar et al. 2002; Lacy et al. 2004; Schram et al. 2004; Cheng et al. 2007). Taken together with

findings from the present study, the weight of evidence suggests AI may not provide a valid indication of central arterial stiffness in stage 5 CKD, which is characterised by advanced average age and high prevalence of diabetes. Although AI is predictive of mortality in stage 5 CKD (London et al. 2001a), a larger body of studies supports the predictive utility of PWV in stage 5 CKD and the general population (Verbeke et al. 2011; Vlachopoulos et al. 2010; Blacher et al. 2003; London et al. 2001a). Furthermore, there is evidence that lowering of PWV reduces mortality of maintenance HD patients (Guerin et al. 2001). On balance, PWV is recommended as the preferred method of monitoring central arterial stiffness in the HD population.

7.5.4 Research design considerations - physical function and arterial stiffness

While the sample size met the minimum requirement for multiple regression analysis outlined by Harris (1985) it was lower than the threshold recommended by Tabachnick and Fidell (2007). It is possible that independent contribution of metabolic parameters known to affect vascular function such as diabetes was not significant because of the low percentage of affected participants, increasing type II error risk. Larger cohort studies are recommended to validate multiple regression models presented in the physical function and arterial stiffness chapters. Importantly these studies were cross-sectional, offering a contemporaneous snapshot of correlates of arterial stiffness, and therefore causation cannot be inferred. In addition candidate biomarkers for multivariable analysis were limited to routine clinical health indices due to resource and budgetary constraints. Consequently, the discussion regarding physical function and arterial stiffness mechanisms is presented in context of findings from the general literature and remains speculative.

Characteristics of participants in the present study were similar to the international DOPPS project, and broadly representative of the Scottish and UK HD populations except for age, which was six years younger than the median. Notably, individuals who attended for the vascular and physical performance assessments were on average five years younger and had higher DASI scores than the questionnaire only participants. Consequently prevalence and severity of functional capacity impairment for the renal unit as a whole is probably under-represented. It is also speculated the relative contribution of age and perhaps HD vintage to arterial stiffness may be amplified. Therefore findings pertaining to physical function and arterial stiffness should be inferred cautiously to the wider HD population.

Participant uptake is infrequently reported for studies employing physical performance and accelerometer outcomes but appears to be less than 20% (Mercer et al. 1998; Baria et al. 2011). Although the present sample was larger than most single centre observational studies in stage 5 CKD, participants undertaking the assessments represent just 40% (33% with complete datasets) of the Monklands renal unit population. Questionnaire response rate was higher (70%) and similar to that of Mingardi et al. (1999). Uptake reported for these studies reflects a perennial challenge faced by researchers working with clinical populations. North American and European surveys reveal most people agree health research is important but significant barriers to recruitment exist due to: low awareness; low public trust in government bodies; reduced confidence due to media depictions (Getz 2008; Team Consulting 2014). In addition, assessments necessitated a non-dialysis day appointment, which adversely impacted uptake and sample representativeness, and has been observed previously (Johansen et al. 2003a). If research findings and recommendations are to be more inclusive and effective for HD patients most at risk of poor outcomes, then these issues need to be urgently addressed.

Table 7.8 Summary of research considerations arising from chapters 5 and 6.

- Moderate sample size for multivariable analyses increases the risk of type II errors.
- Cross-sectional studies therefore causation cannot be directly inferred.
- Candidate biomarkers limited to routinely obtained clinical indices of health status.
- Sample composed of self-selected participants with younger average age. compared to the resident renal unit and wider HD population.

7.5.5 Recommendations for future vascular research in stage 5 CKD

Clearly, the longer people remain on HD the greater their risk of accelerated vascular aging and premature mortality. This underscores the need for further research regarding health interventions to augment current medical management and reduce the impact of HD as a risk factor. Although these data suggest higher levels of habitual PA may not attenuate arterial stiffness of maintenance HD patients, manipulation of the PA variable via randomised control trial or prospective cohort study at least is necessary to test this hypothesis. Notably, a recent meta-analysis concluded there was evidence that aerobic exercise interventions significantly reduced aortic PWV (Ashor et al. 2014). Moreover, a recently published

pilot study indicates 12 months of thrice weekly aerobic exercise ameliorates aortic stiffness in less severe CKD (Greenwood et al. 2015).

Arteriosclerosis may be irreversible, but the effect of habitual PA on endothelial function, an important functional component of vascular stiffness in other clinical populations (Nigam et al. 2003; Ravikumar et al. 2002; McEniery et al. 2006; Wallace et al. 2007; Bruno et al. 2012) has not been explored in the HD population. Local improvement in endothelial function of HD patients has been observed following forearm strengthening (Rus et al. 2003), but it is not known whether a systemic improvement is provoked by chronic aerobic exercise. The prognostic utility of endothelial function determined by flow-mediated dilatation has been demonstrated in a recent meta-analysis (Xu et al. 2014). It is recommended that future studies investigating the effects of PA interventions on vascular health should include this outcome. Genetic markers implicated in arteriosclerosis and endothelial function should also be considered if the aim is to elucidate PA mediated reductions in CV mortality and morbidity.

Presently there is conflicting evidence regarding improved arterial stiffness following structured PA interventions in stage 5 CKD. Studies are generally uncontrolled or insufficiently powered to detect a clinically meaningful change (Mustata et al. 2004; Toussaint et al. 2008a), or have not stringently regulated the PA stimulus with the objective of improving CRF (Koh et al. 2010). A phase two study in which HD patients were randomly assigned to 12 weeks of intra-dialytic aerobic exercise or an exercise wait-listed control group was also part of this project. Vascular outcome measures were aortic PWV and endothelial function. The study is now closed and it is intended that findings will be disseminated via an independent publication.

Five-year mortality risk associated with CKD increases commensurate with reductions in renal function (Tonelli et al. 2006). Altered vascular structure and greater arterial stiffness has also been observed in people with stage 3 to 4 CKD compared to hypertensive peers with normal renal function (Briet et al. 2006). Moreover, prevalence of left ventricular hypertrophy in people with CKD increases from approximately 40% to 75% by the commencement of RRT (Foley et al. 1995; Levin et al. 1999). Research to determine whether CKD stage is predictive of arterial stiffness could strengthen the case for earlier targeted lifestyle intervention.

The Vicorder device employed in the present study uses oscillometry and carries low operator burden. However, while measures are reliable they differ from those

obtained by applanation tonometry or Doppler flow devices (Hickson et al. 2009; van Leeuwen-Segarceanu et al. 2010; Kis et al. 2011) used in other CKD studies. Agreement between the Vicorder and more frequently used SphygmoCor (AtCor medical. Victoria, Australia) can be improved via a correction equation but values remain significantly different (Hickson et al. 2009). In addition, the prognostic utility of PWV has been demonstrated with devices other than Vicorder. Research exploring the prognostic utility of Vicorder and methods to facilitate comparison of similar vascular outcomes from different devices is warranted.

Table 7.9 Summary of research suggestions arising from chapters 3 to 6.

- Quantify bias of purposive data sampling from just three days accelerometer wear.
- Reliability of PA monitoring technologies available to consumers.
- Calibration studies using artificial neural networks to improve precision of accelerometer categorised PA outcomes specific to the CKD population.
- Calibration studies for ActivPAL categorised PA intensity outcomes.
- Feasibility studies for routine PA monitoring via readily available smart technology.
- Dose-response health benefits of different metrics of objectively measured PA.
- Accelerometer based PA and sedentary time guidelines for health in stage 5 CKD.
- Determine prognostic utility and clinically important thresholds of physical performance tests specific to stage 5 CKD.
- Correlates and relative contribution of PA to Human Activity Profile scores.
- Exploration of interactions between changes in physical function and intermediate endpoints in prospective and intervention studies.
- Effect of medications on phenotypic expression of genes associated with skeletal muscle response to PA.
- Improving uptake of higher levels of PA among people with stage 5 CKD.
- Inclusion of endothelial function as an outcome in PA health and intervention studies.
- Effect of PA on phenotypic expression of genes implicated in arterial stiffness.
- Independent contribution of different levels of CKD severity to arterial stiffness.
- Methods to compare and pool arterial stiffness data obtained via different devices.
- Prognostic utility of Vicorder measured arterial stiffness in stage 5 CKD.

7.6 Conclusions

Assessment of PA via accelerometry is a rapidly expanding field in health research and guidance regarding data reduction criteria is urgently required. Based on the observations of this project, one dialysis day and two non-dialysis days and eight hours wear/day is the minimum required monitor wear time for reliable estimates of PA and sedentary behaviour (normalised to wear time). This rubric should allow 90% sample retention for final analyses thereby preserving ecological validity.

Selection of PA assessment method depends on the information content required. The Stanford Seven-Day Recall provides a broad indication of compliance with consensus PA guidelines but accelerometers are better able to characterise behaviour at the lower end of the activity spectrum, where the majority of the HD population operates. High compliance and low cost of wearable monitors now generally available demonstrates they are a feasible monitoring method.

Similar outcomes from Actigraph GT3x and ActivPAL monitors cannot be used interchangeably in stage 5 CKD. If outcomes of interest are time seated or steps taken, ActivPAL will provide more precise estimates. Until research is undertaken to improve precision of categorised PA outcomes in the CKD population, Actigraph output should be reported as counts per minute only. Subjective and objectively estimated PA show limited agreement in stage 5 CKD due to recognised limitations of both methods, thus precluding direct comparison and pooling of existing data.

Physical function of HD patients is lower than more aged non-uraemic individuals. Habitual PA is the most important independent predictor of physical performance measures of CRF and lower limb neuromuscular function and attenuates the effect of other risk factors. Self-reported functional status outcomes used in this study are unlikely to be sufficiently sensitive to PA behaviour change. A graded scale of physical performance testing can be employed to monitor physical function of young and older HD patients with STS5 and TUAG tasks as the minimum standard. Additional prognostic value of physical performance tests lies in their ability to help identify frail individuals at risk of dependency, hospitalisation and mortality.

In light of high prevalence of functional decline and attendant increase in arterial stiffness with longer HD vintage, uraemia should be viewed as a model of accelerated aging. Habitual PA and higher CRF did not attenuate arterial stiffness of maintenance HD patients suggesting arteriosclerosis is not reversible, however this finding requires verification. Physical activity and CRF mediated benefits on survival

and morbidity in this population may instead be mediated via improved endothelial function and should be explored. Recognised limitations of AI and lack of association with PWV recommend the latter as the preferred arterial stiffness index.

Findings from this project are intended to support renal healthcare providers and allied investigators with selection and standardisation of assessment methods to operationalise current government strategies and KDOQI recommendations. The value of these recommendations cannot be overstated in light of: the growing global health problem of severe kidney disease and substantial attendant burden of care and cost; poor long-term prognosis of stage 5 CKD; poor short-term prognosis for frail individuals initiating HD and those who subsequently become frail.

Table 7.10 Summary of recommendations arising from this thesis for healthcare providers and investigators.

1. **Questionnaires** can be used to screen for compliance with PA guidelines but cannot presently be directly compared to or pooled with objectively estimated PA.
2. **Accelerometry** is feasible for routine PA monitoring and recommended for research seeking to elucidate behaviour mediated mechanisms of health.
3. **ActivPAL and Actigraph GT3x** outcomes are not interchangeable. ActivPAL is preferred for estimating steps taken, time seated, and breaks in sedentary time.
4. **Actigraph GT3x** output should be reported as activity counts per minute only for a gross measure of PA until precision of categorised outcomes is improved.
5. **Wear time:** One dialysis day and two non-dialysis days with eight hours wear per day is the minimum requirement for characterising PA and sedentary behaviour.
6. **Weekend day/s**: Inclusion is not a compulsory data reduction criterion.
7. **Data reduction criteria** should be reported in PA studies for quality assurance.
8. **Physical function**: Physical performance tests are preferred over functional status questionnaires for monitoring changes in PA behaviour and exercise interventions.
9. **Functional status** questionnaires should only be used in tandem with physical performance measures.
10. **Frailty** is easily assessed using expedient physical performance tests.
11. **Sit-to-stand five and Timed up-and-go tests** are the minimum requirement for monitoring physical function in stage 5 CKD.
12. **Healthcare providers** in nephrology now need to move forward with standardisation of physical function monitoring as a ‘sixth vital sign’.
13. **Pulse wave velocity** is the preferred central arterial stiffness index in stage 5 CKD.

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Appendix I a: Ethical approval from West of Scotland Research Ethics Committee.

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 4
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT
www.nhsggc.org.uk

Mr Sean D Prescott
PhD Research Student
Physiotherapy - School of health Sciences
Queen Margaret University
Edinburgh
EH21 6UU

Date 19th August 2011
Your Ref
Our Ref
Direct line 0141 211 2123
Fax 0141 211 1847
E-mail Liz.Jamieson@ggc.scot.nhs.uk

Dear Mr Prescott

Study title: **The relationship of arterial stiffness to physical activity, aerobic fitness and quality of life in people undergoing maintenance haemodialysis therapy for chronic kidney disease. An exploratory study.**
REC reference: **11/WS/0001**
Protocol number: **1**

Thank you for your letter of 02 August 2011, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Appendix I b: Ethical approval from Monklands Hospital R & D department.

NHS Lanarkshire

Mr Sean Prescott
PhD Research Student
Queen Margaret University
School of Health Sciences
Queen Margaret Drive
Edinburgh
EH21 6UU

R&D Department
Corporate Services Building
Monklands Hospital
Monkscourt Avenue
AIRDRIE
ML6 0JS

Date 27 September 2011
Enquiries to Margaret Stewart
R&D Facilitator
Direct Line 01236 712445
Email Margaret.stewart@lanarkshire.scot.nhs.uk

Dear Mr Prescott

PROJECT TITLE: The Relationship of arterial stiffness to physical activity, aerobic fitness and quality of life in people undergoing maintenance haemodialysis therapy for chronic kidney disease. An exploratory study.

R&D ID NUMBER: L11078

I am writing to you as Chief Investigator of the above study to advise that R&D Management approval has been granted for the conduct of your study within Monklands Hospital.

For the study to be carried out you are subject to the conditions outlined overleaf:

I trust these conditions are acceptable to you.

Yours sincerely,

Raymond Hamill
Research & Development Manager

cc.

NAME	TITLE	CONTACT ADDRESS	ROLE
Dr Fiona Coutts	Dean of School of Health Sciences	Queen Margaret University, Queen Margaret University Drive, Edinburgh EH21 6UU	Sponsor Contact

Appendix I c: Study information sheet.

Participant Information Sheet
The relationship of arterial stiffness to physical activity, aerobic fitness, and quality of life in people undergoing maintenance haemodialysis therapy for chronic kidney disease.
Dear Sir/Madam

My name is Sean Prescott and I am a PhD student from the School of Health Sciences at Queen Margaret University in Edinburgh. As part of my PhD degree, I am doing some research projects. One of these will take place at the renal unit in Monklands Hospital. It will look at factors related to arterial health (how well blood vessels work) and quality of life in people receiving haemodialysis.
Before you decide to take part I need to be sure that you understand why this study is taking place, and what would be involved if you agree to take part.

What is the purpose of the study?
Heart problems are often seen with chronic kidney disease and may result in shorter life expectancies. It is believed that this may be due in part to increased arterial stiffness. In the general population higher levels of physical activity and fitness are related to lower arterial stiffness and reduced risk of heart problems. However little is known about relationships between arterial stiffness, physical activity, aerobic fitness in the haemodialysis population. Therefore, the aim of this study is to examine these relationships. It will also look at how quality of life and symptoms might be related to these factors.

Who is able to take part?
The study is open to men and women aged 18 years and over who receive haemodialysis therapy for chronic kidney disease. It is the aim of the research team to involve around 100 people in the study. The study involves some physical activities and a quick assessment will decide if you can take part (form attached).

Do I have to take part?
You do not have to take part. If you decide that you do not wish to continue in the study you may withdraw at any time and you would not have to give a reason. This would not affect the standard of care you receive. You will be withdrawn from the study if you become unwell and are unable to give consent. Any data already collected will be retained.

What will happen if I agree to take part?
You will be asked to come to one appointment at Monklands Hospital renal unit on a non-dialysis day. The session should take no longer than one and a half hours. During this session your arterial stiffness will be measured after you have rested in a lying position for 15 minutes. This is a similar procedure to having your blood pressure taken. We ask that you do not eat or drink beverages containing caffeine such as tea or coffee in the three hours before your appointment, as this may affect measurement of your blood pressure and arterial stiffness. Alcohol can also affect these measures so please do not drink alcohol in the 10 hours before your appointment.
Your height and weight will be measured and you will be given two short questionnaires on your current fitness level. These should take no longer than five minutes each to complete. You will also be asked to do the following three short physical activities: measuring your grip strength; standing up from a seated position five times; and getting up from a chair to walk three metres, return and sit down again. These activities will take 5-10 minutes to do.

The final activity is a graded shuttle walk on a short 10-metre course marked with cones. You will hear beeps that will pace you and prompt you to walk a bit quicker each minute until you decide to stop. Usual time for the shuttle walk is 5-12 minutes. You do not have to do this activity if you choose not to. The session will progress at a pace comfortable for you and allow time for rest periods. At the end of this session you will be given two small activity monitors to wear. One is attached on a belt and is to be worn during waking hours. The other monitor, which is similar in size to a credit card is positioned on the front of your thigh with non-allergenic tape and may be worn at night. Both monitors are to be worn over the following 8 days.

Over the next three dialysis sessions you will be asked to complete three questionnaires. One questionnaire is on physical activity and the other two will ask you about aspects of quality of life and experience of symptoms with your condition. These will take approximately 10-20 minutes each to complete. The questionnaires do contain some personal questions. You do not have to answer these if you choose not to. The activity monitor will be collected after nine days when you come to the renal unit for dialysis.

What if I would like to take part but have no personal transport or have special transport needs?

If you need help with transport to attend the non-dialysis appointment a taxi can be arranged and you will be reimbursed for travel costs.

How can I find out more information about this study?

You can speak with me as the researcher. You are also welcome to contact Dr Claire Nolan, an independent person, who knows about this project but is not involved in it. Dr Nolan is a consultant nephrologist at Monklands Hospital. Her contact details are given at the end of this information sheet.

What are the possible risks or disadvantages of taking part?

Measurement of arterial stiffness and the physical activities used in the study will present little or no risk to you. There may be a small disruption to your daily routine in that you will be asked to make one visit to the renal unit outside of your normal times. However, this will be for one session only and will be at a time agreed between you and the researcher. Use of the activity monitor requires only that you remember to attach it to your belt during the day for 8 days.

What are the benefits of taking part?

There will be no immediate benefits to taking part in the study. However your taking part will help further knowledge about how physical activity and fitness might influence heart health and relate to quality of life. The project will be valuable as it will help guide improvements in health care and quality of life for this condition.

What if there is a problem?

If you have any concerns about any part of this study, you can speak with me as the researcher in the first instance or Dr Nolan. If you remain unhappy and wish to complain formally, you may do this by contacting: Dr Fiona Coutts, Dean of Health Sciences Queen Margaret University (details at end of information sheet); or through the NHS Complaints Procedure (details can be obtained from the hospital).

Will my taking part be kept confidential?

Your GP will be informed that you are taking part in the study, however all information about your taking part will be kept strictly confidential. If any concerns regarding your health arise during the study your medical team will be informed. Your name will be replaced with a unique code. It will not be possible for you to be identified in any reporting of the data gathered. The information collected will be for the researcher and the research team's use only and will be stored securely according to the Data Protection Act 1998. The study data will be destroyed on completion of the study.

What will happen to the results of the study?

The results will be used for presentation in a PhD thesis and may be published in a journal or presented at a conference. A summary of the information will be made available to you if you wish. You will not be identified in any publication or report.

Who is organising and funding the research?

This research is being organised by Professor Tom Mercer from Queen Margaret University (tmercer@qmu.ac.uk) and Dr Jamie Traynor and Dr Ilona Shilliday from Monklands Hospital. The project is being jointly funded by the UK Kidney Patients Foundation and Queen Margaret University.

Who has reviewed this study?

This study has been examined by the West of Scotland Research Ethics Committee, which has responsibility for protecting your safety, rights, wellbeing and dignity. It has met the standards set by this body and given a favourable ethical opinion.

If you have read and understood this information sheet, and any questions you had have been answered, please now see the consent forms if you would like to take part in the study. You may keep one of the consent forms for your own records.

Thank you for considering taking part in this study.

Yours sincerely

Sean Prescott

Contact Information

<table>
<tr>
<td>Sean Prescott, PhD Research Student,
Physiotherapy, Health Sciences
Queen Margaret University, Edinburgh
Musselburgh
East Lothian EH21 6UU
Email / Telephone: sprescott@qmu.ac.uk / 0131 474 0000</td>
<td>Dr Fiona Coutts
Dean of Health Sciences
Queen Margaret University, Edinburgh
Musselburgh
East Lothian EH21 6UU
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</tr>
<tr>
<td colspan="2">Independent adviser
Dr Claire Nolan
Consultant Nephrologist
Monklands Hospital
Monkscourt Avenue
Airdrie
ML6 0JS
Email / Telephone: claire.nolan@lanarkshire.scot.nhs.uk / 0123 671 3167</td>
</tr>
</table>

Appendix I d: Participant consent form.

Title of Project: The relationship of arterial stiffness to physical activity, aerobic fitness and quality of life in people undergoing maintenance haemodialysis therapy for chronic kidney disease

Name of Researcher: Sean Prescott
Contact phone: 0131 474 0000 email: sprescott@qmu.ac.uk

Please initial box

1	I confirm that I have read and understand the information sheet dated _____ for the above study. I have had the chance to think over the information and ask questions. The answers I have received have been satisfactory.	☐
2	I understand that my taking part is voluntary and that I am free to withdraw at any time, without giving a reason. I understand that my medical care will not be affected.	☐
3	I agree to attend the renal unit on a non-dialysis day for the purpose of the study.	☐
4	I recognise that I should alert the researcher straight away if I feel any dizziness, chest pain, joint pain or any other physical discomfort whilst completing the physical activities.	☐
5	I agree to take part in the above study.	☐
6	I agree to my GP being informed of my taking part in the study.	☐
7	I understand that this is part of PhD project that will result in a thesis to be marked and presented at a conference and/or in a journal publication.	☐
8	I wish to be sent a copy of final research findings.	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Researcher	Date	Signature

3 copies: 1 for researcher, 1 for participant and 1 to be kept with hospital notes
Version 2. 19/07/2011 Sean Prescott

Appendix I e: Participant recruitment pamphlet.

NHS Lanarkshire

Monklands Hospital is starting a project on health and quality of life in people receiving dialysis therapy. It will look at how physical activity and capacity to do activities of daily life relate to arterial health and experience of chronic kidney disease. The aim of the research is to increase knowledge of this condition. This is so the team working with you can continue to design a service and provide care that best fits you.

You need to be aged 18 years and over and attend Monklands Hospital regularly for dialysis. If that is you then feel welcome to contact us for more information.

You will be asked to come to the hospital once outside your normal visits. If you require help with transport this can be arranged. This visit is for measurement of arterial health using pressure cuffs (like those used for blood pressure). Two questionnaires and several short physical activities will be used to record your capacity to do tasks of daily life. This visit will be paced for your comfort and last around one and a half hours. You will also be asked to wear two small activity monitors for about a week. When you return to the renal unit for regular dialysis you will be given three questionnaires. These will be spread over three visits and cover quality of life, symptom experience and daily activity. This will all take place over 9 days.

This is a unique chance to help others with the same condition and be part of designing your health service. This project is funded by the UK Kidney Patients Foundation and Queen Margaret University.

If you wish to find out more on the project for your health service please feel welcome to contact:

1. A member of your medical team at Monklands Hospital renal unit.
2. Dr Claire Nolan, Consultant Nephrologist at Monklands Hospital renal unit. Dr Nolan is an independent person who knows about the project.
   Email / Telephone: claire.nolan@lanarkshire.scot.nhs.uk / 0123 671 3167
3. Sean Prescott, Physiotherapist and researcher from Queen Margaret University.
   Email / Telephone: sprescott@qmu.ac.uk / 0131 474 0000

Appendix II: BORG's rating of perceived exertion scale.

Borg's Rating of Perceived Exertion Scale

6	**No exertion at all**
7 **8**	**Extremely light**
9 **10**	**Very light**
11 **12**	**Light**
13 **14**	**Somewhat hard**
15 **16**	**Hard (heavy)**
17 **18**	**Very Hard**
19	**Extremely hard**
20	**Maximal exertion**

Instructions: When you begin doing aerobic exercise, try to estimate how hard you feel the work is; that is, rate the degree of the perceived level of exertion you feel. Think of perceived exertion as the total amount of exertion and physical fatigue, combining all sensations and feelings of physical stress, effort, and fatigue. When rating how the whole body is feeling while exercising don't concern yourself with any one factor such as leg pain, shortness of breath or work intensity, simply try to concentrate on your total inner feeling of exertion. Try to estimate as honestly and objectively as possible. Don't underestimate the degree of exertion you feel, but don't overestimate it either. Just try to estimate as accurately as possible (Borg 1998).

Appendix III: Duke activity status index questionnaire.

Duke Activity Status Index (DASI)

Item	Activity – Can you…..	Yes	No
1	take care of yourself (eating dressing bathing or using the toilet)?		
2	walk indoors such as around your house?		
3	walk a block or two on level ground?		
4	climb a flight of stairs or walk up a hill?		
5	run a short distance?		
6	do light work around the house like dusting or washing dishes?		
7	do moderate work around the house like vacuuming sweeping floors or carrying in groceries?		
8	do heavy work around the house like scrubbing floors or lifting and moving heavy furniture?		
9	do yardwork like raking leaves weeding or pushing a power mower?		
10	have sexual relations?		
11	participate in moderate recreational activities like golf bowling dancing doubles tennis or throwing a baseball or football?		
12	participate in strenuous sports like swimming singles tennis football basketball or skiing?		

Answers are expressed as yes or no response with a 1 representing yes and 0 representing a no response. The responses are then multiplied by the weight value for each question and a composite score obtained.

Duke activity status index = SUM(values for all 12 questions)

Interpretation:

• maximum value 58.2

• minimum value 0

Estimated peak oxygen uptake in mL/min = (0.43 * (duke activity status index)) + 9.6

Reference:

Hlatky MA Boineau RE et al. 1989 A brief self-administered questionnaire to determine functional capacity (The Duke Activity Status Index). American Journal of Cardiology. 64: 651-654.

Appendix IV: Leicester uraemic symptom scale (part 1).

THE LEICESTER URAEMIC SYMPTOM SCALE (LUSS)

Part 1

The following is a list of 10 symptoms commonly associated with kidney problems. Please tick the box which best describes how frequently you experience each symptom.

SYMPTOM	Never	Less than once per week	1-2 times per week	Several times per week	Every day
Itching					
Sleep disturbance					
Loss of appetite					
Excessive tiredness					
Pain in bones/joints					
Poor concentration/ mental alertness					
Loss of muscle strength/ power					
Shortness of breath					
Muscle spasm/stiffness					
Restless legs					

Appendix IV continued: Leicester uraemic symptom scale (part 2).

LUSS Part 2

Some of the symptoms that you ticked overleaf may be more intrusive than others. Please tick the boxes below which best describe how intrusive you find each symptom.
If you do not experience a symptom, please tick the box marked N/A (not applicable).

SYMPTOM	N/A	Not at all intrusive	Slightly intrusive	Quite intrusive	Very intrusive	Extremely intrusive
Itching						
Sleep disturbance						
Loss of appetite						
Excessive tiredness						
Pain in bones/joints						
Poor concentration/ mental alertness						
Loss of muscle strength/power						
Shortness of breath						
Muscle spasms/stiffness						
Restless legs						

Thank you for completing this questionnaire

For office use only:

SCORE TABLE	
No. of uraemic symptoms identified	
Part 1 Total Score	
Part 2 Total Score	

Appendix V a: Actigraph and ActivPAL wear instructions.

Activity Monitors

Thank you for wearing the activity monitors. They record different aspects of physical activity such as how much time you spend sitting, standing or walking. Please wear the monitors during waking hours for eight days including weekdays and weekends. You can take the monitors off at night when you go to bed, but please try to remember to put them on in the morning as soon as possible after you get up. The monitors must be removed for showering/bathing/swimming, but should be put back on immediately after.

Both monitors record 8 days of activity starting from the time you were given them so please wear them from the day you receive them.

After you have worn the monitors for eight days, please bring them back to the dialysis unit during your routine appointment on _____ and I will arrange to collect them.

Wearing the Actigraph

The Actigraph is worn on the belt provided with the monitor place on the non-dominant hip, just above the boney point on the front of your pelvis. Please wear it with the wording on the monitor right side up.

Applying the ActivPAL

Please attach the monitor to the front of your thigh on the same side as the Actigraph. It should be positioned on the midline of the thigh, between the hip and the knee in the orientation indicated by the figure on the front panel of the monitor (the little man should be standing pointing upwards).

You have been provided with special stickies to be used with the monitor, one for each day. The backings on the stickies indicate which side is to be attached to the monitor and which side adheres to your skin. The stickies can be removed and repositioned so when you remove the monitor to shower you should be able to put it back on using the same stickie.

The activity monitors and tape are **not waterproof** and they should be **removed for bathing or swimming**. The skin should be thoroughly dried after bathing to maximise the adherence of the tape/gel. Further details can be found on the PALstickies instruction sheet provided.

You've also been given some Hypafix tape. This can be used over the monitor, in addition to the stickies if you feel the monitor is not secure enough.

Finally, please return the included form and note when you wore the monitors.

If you have any questions regarding the monitor please contact me on 0131 4740000 say: 'Sean Prescott'. You can also reach me at 07980338486.

Thank you very much for helping with this study,

Sean

Appendix V b: ActivPAL and Actigraph wear log.

ActivPAL and Actigraph Usage

	Date	Time On	Time Off
Day 1			
Day 2			
Day 3			
Day 4			
Day 5			
Day 6			
Day 7			
Day 8			

Comments:

Please fill in the date and the times above and return with the monitor in the addressed envelope

Appendix VI: Stanford Seven-Day Recall questionnaire.

Stanford 7-day Physical Activity Recall SSN

PAR#: 1 2 3 4 5 6 7 Participant _____

Interviewer _____Today is _____ Today's date _____

1. Were you employed in the last seven days? 0. No (Skip to Q#4) 1. Yes

2. How many days in the last seven did you work? ____ days

3. How many total hours did you work in the last seven days? ____ hours last week

4. What two days do you consider your weekend days? _____
(mark days below with a squiggle)

WORKSHEET DAYS

	SLEEP	1____	2____	3____	4____	5____	6____	7____
MORNING	Moderate							
	Hard							
	Very Hard							
AFTERNOO	Moderate							
	Hard							
	Very Hard							
EVENING	Moderate							
	Hard							
	Very Hard							
Total Min Per Day	Strength:							
	Flexibility:	_____	_____	_____	_____	_____	_____	_____

4a. Compared to your physical activity over the past 3 months, was last week's physical activity more, less, or about the same? 1. More 2. Less 3.About the same	6. Do you think this was a valid PAR interview? 1. Yes 0. No If NO, go to the back and explain
5. Were there any problems with the PAR interview? 0. No 1. Yes If YES, go to the back and explain	7. Were there any special circumstances concerning the PAR? 0. No 1. Yes, If YES, what were they? (circle) 1. Injury all week 2. Illness all week 3. Illness part week 4. Injury part week 5. Pregnancy 6. Other:

Appendix VI b: Stanford Seven Day Recall interview script.

Introduction

The next set of questions that I will be asking you refers to the physical activities you've engaged in during the past week.

Work

I am going to start by asking you a few questions about your employment. (*Ask employment questions on top of PAR worksheet.*)

Weekend Days

What 2 d of the week do you consider to be your weekend days? Most people consider Sat. and Sun. to be their weekend days, but it may be different for you.

Record the 2 weekend days in the space provided on the worksheet and draw squiggly lines through the 2 weekend days.

Sleep

Now I'd like to look at the time you spent sleeping in the past week. By sleeping, I mean the time you went to bed one night and the time that you got out of bed the next morning. You may not necessarily have been asleep the entire time you were in bed. You may have been reading or watching television.

Today is (i.e., Monday), so yesterday was (i.e., Sunday).

What time did you go to bed (Sunday) night and get up (Monday) morning?

Do this for each day of the 7-d recall. Write down days of week and sleep times reported by the participant in the space provided on the top of the worksheet. Calculate total time spent sleeping after completing the interview.

Physical Activity

I am going to ask you about the physical activities you engaged in during the past 7 d, starting with yesterday and going back 7 d. In doing so, please remember, this is a recall of actual activities for the past week, not a history of what you usually do.

We are not considering light activities, such as desk work, standing, light housework, softball, and bowling. We are considering occupational, household, recreational, and sports activities that make you **feel** similar to how you feel when you are walking at a normal pace. For example, slow stop-and-go walking such as window shopping, is **not** included; however, walking at a normal pace to do an errand is included.

Intensity Guidelines

I will ask you to categorize the intensity of each physical activity you do into one of three groups, moderate, hard, or very hard:

- The moderate category is similar to how you **feel** when you're **walking at a normal pace**.
- The very hard category is similar to how you **feel** when you are **running**.
- The hard category just falls in between.
- In other words, if the activity seems harder than walking but not as strenuous as running, it should go in the hard category.

Segments of the Day

I am going to ask you about the physical activities you engaged in during three segments of the day, which includes morning, afternoon, and evening. Morning is considered from the time you get up in the morning to the time you have lunch; afternoon is from lunch to dinner; and evening is from dinner until the time you go to bed.

Setting the Stage

Getting people to think about their day in general will help them remember all of their activities. Always spend some time "setting the stage" for each day.

Today is (i.e., Monday), so yesterday was (i.e., Sunday). Think about what you did (Sunday) morning. **Where were you? Think about what you usually do. Did you do anything unusual?** Did you do any physical activity (Sunday morning)?

Appendix VI b: Stanford Seven Day Recall script continued.

Duration

The activity in question should be performed for a total of 10 min, intermittently or continuously, during one segment of the day, morning, afternoon, or evening (except for strength and flexibility, in which the total amount of minutes is recorded)

How long did you do that activity?

Make sure that the activity excludes the time that they stood still or took breaks.

How much of that time was spent standing still or taking **breaks**?

Intensity

Always refer to intensity guidelines: "Did that activity feel similar to how you feel when you are walking or running or is it somewhere in between?"

Did that activity make you feel similar to how you feel when you are walking or running, or is it somewhere in between? (How would you rate the intensity of that activity? Did it feel similar to how you feel when you walk or run or somewhere in between? Keep in mind that a moderate intensity feels similar to walking at a normal-to-brisk pace, and very hard feels similar to running.) Think about what you did **in general** (Sun) afternoon. Did you do any physical activity?

Record the total number of minutes spent doing strength activities and the total minutes spent doing flexibility activities separately for each day. Make sure that the activity excludes the time during which the participant or stood still or took breaks.

Now I am going to ask you about activities you might do for building strength or improving flexibility. Strength activities include push-ups, pull-ups, sit-ups, lifting free weights, and using weight machines. Flexibility activities include holding stretches for several seconds and yoga. Did you do any strength or flexibility activities? How many minutes did you spend on each? (*Record separately at the bottom of the worksheet.*)

At the End of Each Day Ask

Are there any physical activities **that you might have forgotten**? Did you do any physical activity at work? any other recreational or sport activities? housework or gardening? Were there any other walks that you might have taken?

On the Last Day of Recall Ask

Take a moment to think back over the course of the week and think of any activities that you may have forgotten.

Last Question

The last question I am going to ask you is, "Compared to your physical activity over the past 3 mo, was last week's physical activity more, less, or about the same?"

Record answer on bottom of worksheet.

Summary

- Ask about the subject's physical activity during each segment of the day for each of the 7 d of the recall.
- Start with the previous day and go backwards. Record each day's recall in turn.
    a. Set the stage by having participants recall what they did in general.
    b. Record separately for the morning, the afternoon, and the evening.
    c. Ask if they missed any activities.
- After each day be sure to ask about strength and flexibility and about any activities that may have been forgotten.
- Record everything on the worksheet.
- Record on the worksheet the time and the intensity of the activity. Make sure to record the activity on the worksheet in the correct segment of the day.
- Complete the 7-Day PAR interview by asking the question at the bottom of the worksheet regarding physical activity over the past 3 mo.
- On the back of the worksheet, answer the questions and note anything the participant stated that might be helpful in interpreting the data.
- It is OK for the subject to add or change a previous report later in the interview.

Appendix VII: Normality of Actigraph physical activity data.

Actigraph outcome variables. Participants with seven days wear greater than four hours wear/day.

	7 days			Dialysis Days			Non-Dialysis Days		
	Statistic	df	Sig.	Statistic	df	Sig.	Statistic	df	Sig.
Wear (min)	0.099	51	0.200*	0.065	51	0.200*	0.071	51	0.200*
Sedentary (min)	0.054	51	0.200*	0.067	51	0.200*	0.082	51	0.200*
Sedentary (%)	0.126	51	0.042	0.125	51	0.046	0.106	51	0.200*
MVPA (min)	0.245	51	0.000	0.296	51	0.000	0.236	51	0.000
MVPA (%)	0.242	51	0.000	0.263	51	0.000	0.226	51	0.000
TPA (min)	0.125	51	0.045	0.151	51	0.005	0.100	51	0.200*
TPA (%)	0.126	51	0.042	0.125	51	0.046	0.106	51	0.200*
Uniaxial cpd	0.209	51	0.000	0.269	51	0.000	0.180	51	0.000
Uniaxial cpm	0.197	51	0.000	0.197	51	0.000	0.208	51	0.000
Triaxial cpd	0.165	51	0.001	0.217	51	0.000	0.155	51	0.004
Triaxial cpm	0.175	51	0.000	0.168	51	0.001	0.187	51	0.000
Step count/day	0.192	51	0.000	0.276	51	0.000	0.183	51	0.000
Step count/min	0.201	51	0.000	0.237	51	0.000	0.222	51	0.000

*Lower bound of true significance (Kolmogorov-Smirnov test)
cpd = counts per day, cpm = counts per minute

Actigraph PA variables. Participants with three dialysis days wear or four non-dialysis days wear greater than four hours/day.

	Dialysis Days (n = 63)			Non-Dialysis Days (n = 54)		
	Statistic	df	Sig.	Statistic	df	Sig.
Wear (min)	0.066	63	0.200*	0.074	54	0.200*
Sedentary (min)	0.071	63	0.200*	0.088	54	0.200*
Sedentary (%)	0.133	63	0.008	0.102	54	0.200*
MVPA (min)	0.265	63	0.000	0.229	54	0.000
MVPA (%)	0.238	63	0.000	0.218	54	0.000
TPA (min)	0.153	63	0.001	0.096	54	0.200*
TPA (%)	0.133	63	0.008	0.102	54	0.200*
Uniaxial cpd	0.230	63	0.000	0.160	54	0.001
Uniaxial cpm	0.179	63	0.000	0.201	54	0.000
Triaxial cpd	0.204	63	0.000	0.139	54	0.011
Triaxial cpm	0.160	63	0.000	0.165	54	0.001
Step count/day	0.240	63	0.000	0.158	54	0.002
Step count/min	0.205	63	0.000	0.192	54	0.000

*Lower bound of true significance (Kolmogorov-Smirnov test)
cpd = counts per day, cpm = counts per minute

Appendix VIII: Normality of ActivPAL physical activity data.

ActivPAL outcome variables. Participants with seven days wear greater than four hours wear/day

	7 days			Dialysis Days			Non-Dialysis Days		
	Statistic	df	Sig.	Statistic	df	Sig.	Statistic	df	Sig.
Wear minute	0.982	44	0.722	0.982	44	0.726	0.976	44	0.490
Sit/Lie (min)	0.964	44	0.176	0.991	44	0.978	0.945	44	0.037
Sit/Lie (%)	0.933	44	0.014	0.875	44	0.000	0.927	44	0.008
Step time (min)	0.729	44	0.000	0.571	44	0.000	0.832	44	0.000
Step time (%)	0.741	44	0.000	0.708	44	0.000	0.771	44	0.000
Stand time (min)	0.954	44	0.076	0.835	44	0.000	0.961	44	0.141
Stand time (%)	0.933	44	0.014	0.875	44	0.000	0.927	44	0.008
Steps (day)	0.759	44	0.000	0.639	44	0.000	0.829	44	0.000
Steps (min)	0.761	44	0.000	0.748	44	0.000	0.772	44	0.000
Transitions (day)	0.978	44	0.561	0.971	44	0.336	0.972	44	0.369
Transitions (hour)	0.893	44	0.001	0.949	44	0.051	0.895	44	0.001
METmin (day)	0.987	44	0.893	0.918	44	0.004	0.962	44	0.161
METmin (min)	0.792	44	0.000	0.781	44	0.000	0.805	44	0.000

Shapiro-Wilk test of normality

ActivPAL outcome variables. Participants with either three dialysis days wear or four non-dialysis days wear greater than four hours/day

	Dialysis Days[†]			Non-Dialysis Days[††]		
	Statistic	df	Sig.	Statistic	df	Sig.
Wear minute	0.071	55	0.200*	0.970	47	0.261
Sit/Lie (min)	0.048	55	0.200*	0.950	47	0.043
Sit/Lie (%)	0.088	55	0.200*	0.931	47	0.009
Step time (min)	0.230	55	0.000	0.846	47	0.000
Step time (%)	0.233	55	0.000	0.792	47	0.000
Stand time (min)	0.125	55	0.033	0.964	47	0.151
Stand time (%)	0.088	55	0.200*	0.932	47	0.009
Steps (day)	0.233	55	0.000	0.845	47	0.000
Steps (min)	0.260	55	0.000	0.793	47	0.000
Transitions (day)	0.119	55	0.049	0.975	47	0.391
Transitions (hour)	0.098	55	0.200*	0.906	47	0.001
METmin (day)	0.082	55	0.200*	0.962	47	0.133
METmin (min)	0.226	55	0.000	0.824	47	0.000

*Lower bound of true significance

[†] Dialysis Days n = 55 Kolmogorov-Smirnov normality test

[††] Non-Dialysis Days n =47 Shapiro-Wilk normality test

Appendix IX: Test of differences for Actigraph outcome variables. Dialysis versus non-dialysis days.

Wear time	>4 hours	>5 hours	>6 hours	>7 hours	>8 hours	>9 hours	>10 hours
n =	51	49	49	47	37	35	29
Wear time (min)	t(50) = 11.40 p < 0.001 d = 1.60	t(48) = 12.90 p < 0.001 d = 1.84	t(48) = 12.90 p < 0.001 d = 1.84	t(46) = 12.40 p < 0.001 d = 1.81	t(36) = 11.40 p < 0.001 d = 1.87	t(34) = 11.31 p < 0.001 d = 1.91	t(28) = 10.68 p < 0.001 d = 1.98
Sedentary time (min)	t(50) = 8.69 p < 0.001 d = 1.22	t(48) = 8.57 p < 0.001 d = 1.22	t(48) = 8.57 p < 0.001 d = 1.22	t(46) = 8.21 p < 0.001 d = 1.20	t(36) = 7.18 p < 0.001 d = 1.18	t(34) = 7.11 p < 0.001 d = 1.20	t(28) = 6.52 p < 0.001 d = 1.21
Sedentary time (%)	Z = -5.04 p < 0.001 r = 0.71	Z = -4.85 p < 0.001 r = 0.69	Z = -4.85 p < 0.001 r = 0.69	Z = -4.68 p < 0.001 r = 0.68	Z = -3.99 p < 0.001 r = 0.66	Z = -4.01 p < 0.001 r = 0.68	Z = -3.75 p < 0.001 r = 0.70
MVPA time (min)	Z = -2.89 p = 0.004 r = 0.40	Z = -3.01 p = 0.003 r = 0.43	Z = -3.01 p = 0.003 r = 0.43	Z = -3.00 p = 0.003 r = 0.44	Z = -2.50 p = 0.013 r = 0.41	Z = -2.65 p = 0.008 r = 0.45	Z = -2.24 p = 0.025 r = 0.42
MVPA time (%)	Z = -3.21 p = 0.001 r = 0.45	Z = -3.23 p = 0.001 r = 0.46	Z = -3.23 p = 0.001 r = 0.46	Z = -3.22 p = 0.001 r = 0.47	Z = -2.30 p = 0.021 r = 0.38	Z = -2.51 p = 0.012 r = 0.42	Z = -2.20 p = 0.028 r = 0.41
LVPA time (min)	Z = -2.93 p = 0.003 r = 0.41	Z = -3.12 p = 0.002 r = 0.45	Z = -3.12 p = 0.002 r = 0.45	Z = -3.08 p = 0.002 r = 0.45	Z = -3.18 p = 0.001 r = 0.52	Z = -3.23 p = 0.001 r = 0.55	Z = -2.93 p = 0.003 r = 0.54
LVPA time (%)	Z = -5.04 p < 0.001 r = 0.71	Z = -4.85 p < 0.001 r = 0.69	Z = -4.85 p < 0.001 r = 0.69	Z = -4.68 p < 0.001 r = 0.68	Z = -3.99 p <0.001 r = 0.66	Z = -4.01 p <0.001 r = 0.68	Z = -3.75 p <0.001 r = 0.70
Uniaxial Counts/day	Z = -3.403 p = 0.001 r = 0.48	Z = -3.59 p < 0.001 r = 0.51	Z = -3.59 p < 0.001 r = 0.51	Z = 3.52 p < 0.001 r = 0.51	Z = -3.18 p = 0.001 r = 0.52	Z = -3.24 p = 0.001 r = 0.55	Z = -2.91 p = 0.004 r = 0.60
Uniaxial Counts/min	Z = -4.705 p <0.001 r = 0.66	Z = -4.49 p < 0.001 r = 0.64	Z = -4.49 p < 0.001 r = 0.64	Z = -4.349 p < 0.001 r = 0.63	Z = -3.61 p < 0.001 r = 0.59	Z = -3.65 p < 0.001 r = 0.62	Z = -3.32 p = 0.001 r = 0.62
Triaxial Counts/day	Z = -3.77 p < 0.001 r = 0.53	Z = -3.99 p <0.001 r = 0.57	Z = -3.99 p <0.001 r = 0.57	Z = 3.852 p <0.001 r = 0.56	Z = -3.75 p <0.001 r = 0.62	Z = -3.77 p <0.001 r = 0.64	Z = -3.49 p <0.001 r = 0.65
Triaxial Counts/min	Z = -5.54 p < 0.001 r = 0.78	Z = -5.38 p < 0.001 r = 0.77	Z = -5.38 p < 0.001 r = 0.77	Z = -5.21 p <0.001 r = 0.76	Z = -4.64 p < 0.001 r = 0.76	Z = -4.65 p < 0.001 r = 0.79	Z = -4.23 p < 0.001 r = 0.78
Step count/day	Z = -3.05 p = 0.002 r = 0.43	Z = -3.19 p < 0.001 r = 0.46	Z = -3.19 p <0.001 r = 0.46	Z = -3.19 p = 0.001 r = 0.46	Z = -2.95 p = 0.003 r = 0.48	Z = -3.05 p = 0.002 r = 0.52	Z = -2.63 p = 0.009 r = 0.49
Step count/min	Z = -4.04 p < 0.001 r = 0.57	Z = -3.92 p < 0.001 r = 0.56	Z = -3.92 p < 0.001 r = 0.56	Z = -3.83 p < 0.001 r = 0.56	Z = -3.36 p = 0.001 r = 0.55	Z = -3.44 p = 0.001 r = 0.58	Z = -3.02 p = 0.003 r = 0.56

Appendix X. Test of differences for ActivPAL outcome variables. Dialysis versus Non-Dialysis days.

Wear time	**>4 hours**	**>5 hours**	**>6 hours**	**>7 hours**	**>8 hours**	**>9 hours**	**>10 hours**
n =	44	42	39	38	35	32	22
Wear (min)	$T_{(43)}$=5.565 p < 0.001 d = 1.20	t(41) = 5.508 p < 0.001 d = 1.22	t(38) = 5.719 p < 0.001 d = 1.32	t(37) = 5.750 p < 0.001 d = 1.34	t(34) = 5.496 p < 0.001 d = 1.33	t(31) = 4.752 p < 0.001 d = 1.21	t(21) = 3.274 p < 0.001 d = 1.01
Sit/Lie (min)	Z = -5.532 p < 0.001 r = 0.83	Z = -5.383 p < 0.001 r = 0.83	Z = -5.233 p < 0.001 r = 0.84	Z = -5.156 p < 0.001 r = 0.84	Z = -4.914 p<0.001 r = 0.83	Z = -4.656 p< 0.001 r = 0.84	Z = -4.010 p < 0.001 r = 0.85
Sit/Lie (%)	Z = -5.053 p < 0.001 r = 0.76	Z = -4.870 p < 0.001 r = 0.75	Z = -4.856 p < 0.001 r = 0.78	Z = -4.764 p < 0.001 r = 0.77	Z = -4.472 p < 0.001 r = 0.76	Z = -4.637 p < 0.001 r = 0.82	Z = -4.107 p < 0.001 r = 0.88
Stand (min)	Z = -4.260 p < 0.001 r = 0.64	Z = -4.508 p < 0.001 r = 0.70	Z = -4.410 p < 0.001 r = 0.71	Z = -4.300 p < 0.001 r = 0.70	Z = -4.013 p < 0.001 r = 0.68	Z = -4.544 p < 0.001 r = 0.80	Z = -3.977 p < 0.001 r = 0.85
Stand (%)	Z = -5.053 p < 0.001 r = 0.76	Z = -4.870 p < 0.001 r = 0.75	Z = -4.856 p < 0.001 r = 0.78	Z = -4.764 p < 0.001 r = 0.77	Z = -4.472 p < 0.001 r = 0.76	Z = -4.637 p < 0.001 r = 0.82	Z = -4.107 p < 0.001 r = 0.88
Step Time (min)	Z = -3.980 p < 0.001 r = 0.60	Z = -4.245 p < 0.001 r = 0.66	Z = -4.117 p < 0.001 r = 0.66	Z = -4.010 p < 0.001 r = 0.65	Z = -3.653 p < 0.001 r = 0.62	Z = -4.207 p < 0.001 r = 0.74	Z = -3.847 p < 0.001 r = 0.82
Step Time (%)	Z = -4.878 p < 0.001 r = 0.74	Z = -4.683 p < 0.001 r = 0.72	Z = -4.591 p < 0.001 r = 0.74	Z = -4.488 p < 0.001 r = 0.73	Z = -4.193 p < 0.001 r = 0.71	Z = -4.376 p < 0.001 r = 0.77	Z = -3.912 p < 0.001 r = 0.83
Transitions (day)	$T_{(43)}$= -2.842 p = 0.007 d = 0.61	$T_{(41)}$= -3.525 p =0.001 d = 0.78	$T_{(38)}$= -4.132 p < 0.001 d = 0.95	$T_{(37)}$= -3.974 p < 0.001 d = 0.92	$T_{(34)}$= -4.212 p < 0.001 d = 1.02	$T_{(31)}$= -3.908 P < 0.001 d = 0.99	$T_{(21)}$= -4.778 p < 0.001 d = 1.47
Transitions (hr)	Z = -5.123 p < 0.001 r = 0.77	Z = -4.983 p < 0.001 r = 0.77	Z = -5.177 p < 0.001 r = 0.83	Z = -5.098 p < 0.001 r = 0.83	Z = -4.848 p < 0.001 r = 0.82	Z = -4.581 p < 0.001 r = 0.81	Z = -3.912 p < 0.001 r = 0.83
Steps/day	Z = -3.769 p < 0.001 r = 0.57	Z = -3.982 p < 0.001 r = 0.61	Z = -3.852 p < 0.001 r = 0.62	Z = -3.734 p < 0.001 r = 0.61	Z = -3.358 p < 0.001 r = 0.57	Z = -3.964 p < 0.001 r = 0.70	Z = -3.587 p < 0.001 r = 0.76
Steps/min	Z = -4.621 p < 0.001 r = 0.70	Z = -4.408 p < 0.001 r = 0.68	Z = -4.312 p < 0.001 r = 0.69	Z = -4.213 p < 0.001 r = 0.68	Z = -3.882 p < 0.001 r = 0.66	Z = -4.226 p < 0.001 r = 0.75	Z = -3.750 p < 0.001 r = 0.80
METmin/day	Z = -3.349 p = 0.001 r = 0.50	Z = -3.057 p = 0.002 r = 0.47	Z = -3.000 p = 0.003 r = 0.48	Z = -3.125 p = 0.002 r = 0.51	Z = -2.948 p = 0.003 r = 0.50	Z = -2.412 p = 0.016 r = 0.43	Z = -1.347 p = 0.178 r = 0.29
METmin/min	Z = -4.831 p < 0.001 r = 0.73	Z = -4.633 p < 0.001 r = 0.71	Z = -4.549 p < 0.001 r = 0.73	Z = -4.459 p < 0.001 r = 0.72	Z = -4.160 p < 0.001 r = 0.70	Z = -4.506 p < 0.001 r = 0.80	Z = -4.042 p < 0.001 r = 0.86

Appendix XI: Single measure reliability values for Actigraph

Actigraph outcome variables single measure intra-class correlation coefficients **(dialysis days).**

Hours of wear	>4	>5	>6	>7	>8	>9	>10
Cases (n =)	63	63	62	60	57	55	53
Sedentary mins	0.394	0.394	0.452	0.522	0.636	0.614	0.591
Sedentary %	0.771	0.771	0.777	0.801	0.803	0.801	0.806
Total PA mins	0.756	0.756	0.776	0.781	0.786	0.784	0.783
Total PA %	0.799	0.799	0.810	0.814	0.818	0.819	0.818
MVPA mins	0.794	0.794	0.805	0.800	0.796	0.793	0.791
MVPA %	0.776	0.776	0.780	0.776	0.781	0.779	0.779
Triaxial counts/day	0.799	0.799	0.810	0.814	0.818	0.819	0.818
Triaxial counts/min	0.815	0.815	0.818	0.832	0.833	0.834	0.839
Steps/day	0.861	0.861	0.872	0.873	0.869	0.868	0.867
Steps/min	0.860	0.860	0.861	0.867	0.869	0.870	0.871

Actigraph outcome variables single measure intra-class correlation coefficients **(non-dialysis days).**

Hours of wear	>4	>5	>6	>7	>8	>9	>10
Cases (n =)	54	52	52	51	40	38	32
Sedentary mins	0.544	0.524	0.524	0.534	0.595	0.592	0.571
Sedentary %	0.760	0.768	0.768	0.775	0.747	0.744	0.670
Total PA mins	0.746	0.766	0.766	0.770	0.737	0.730	0.701
Total PA %	0.797	0.797	0.797	0.805	0.784	0.791	0.740
MVPA mins	0.811	0.812	0.812	0.821	0.816	0.802	0.805
MVPA %	0.815	0.812	0.812	0.822	0.818	0.808	0.805
Triaxial counts/day	0.796	0.811	0.811	0.811	0.774	0.766	0.761
Triaxial counts/min	0.840	0.838	0.838	0.841	0.821	0.821	0.802
Steps/day	0.841	0.850	0.850	0.850	0.825	0.827	0.821
Steps/min	0.856	0.860	0.860	0.863	0.846	0.852	0.833

Appendix XII: Single measure reliability values for ActivPAL

ActivPAL outcome variables single measure intra-class correlation coefficients **(dialysis days).**

Hours of wear	>4	>5	>6	>7	>8	>9	>10
Cases (n =)	55	55	52	51	51	49	44
Sit/Lie mins	0.459	0.459	0.565	0.591	0.591	0.595	0.689
Sit/Lie %	0.834	0.834	0.834	0.836	0.836	0.829	0.847
Stand mins	0.681	0.681	0.692	0.700	0.700	0.662	0.683
Stand %	0.833	0.833	0.834	0.836	0.836	0.829	0.847
Walking mins	0.743	0.743	0.783	0.795	0.795	0.770	0.781
Walking %	0.766	0.766	0.774	0.781	0.781	0.761	0.769
Steps/day	0.741	0.741	0.788	0.797	0.797	0.773	0.780
Steps/min	0.763	0.763	0.777	0.781	0.781	0.762	0.768
Transitions/day	0.527	0.527	0.582	0.564	0.564	0.535	0.600
Transitions/hr	0.555	0.555	0.592	0.580	0.580	0.569	0.581
METmin/day	0.539	0.539	0.685	0.712	0.712	0.692	0.787
METmin/min	0.812	0.812	0.828	0.831	0.831	0.824	0.852

ActivPAL outcome variables single measure intra-class correlation coefficients **(non-dialysis days).**

Hours of wear	>4	>5	>6	>7	>8	>9	>10
Cases (n =)	47	45	43	43	37	34	24
Sit/Lie mins	0.575	0.540	0.561	0.561	0.496	0.514	0.454
Sit/Lie %	0.697	0.692	0.675	0.675	0.638	0.611	0.667
Stand mins	0.667	0.696	0.657	0.657	0.649	0.585	0.692
Stand %	0.711	0.703	0.647	0.647	0.618	0.584	0.640
Walking mins	0.722	0.740	0.734	0.734	0.718	0.694	0.727
Walking %	0.762	0.757	0.749	0.749	0.727	0.722	0.722
Steps/day	0.749	0.766	0.760	0.760	0.742	0.716	0.733
Steps/min	0.778	0.778	0.770	0.770	0.747	0.739	0.727
Transitions/day	0.538	0.558	0.542	0.542	0.540	0.442	0.406
Transitions/hr	0.652	0.669	0.660	0.660	0.663	0.619	0.560
EE/day	0.367	0.491	0.520	0.520	0.510	0.424	0.544
EE/min	0.772	0.791	0.794	0.794	0.751	0.739	0.725

Appendix XIII Computed wear times Actigraph.

XIII a: Computed wear times Actigraph Sedentary time (mins).

Dialysis Day Sedentary mins					Non-Dialysis Day Sedentary mins				
n =	Wear hours	Days required for desired reliability			n =	Wear hours	Days required for desired reliability		
		0.7	0.8	0.9			0.7	0.8	0.9
63	**4h**	3.59	6.15	13.84	**54**	**4h**	1.96	3.36	7.56
63	**5h**	3.59	6.15	13.84	**52**	**5h**	2.12	3.63	8.17
62	**6h**	2.83	4.85	10.92	**52**	**6h**	2.12	3.63	8.17
60	**7h**	2.14	3.66	8.24	**51**	**7h**	2.04	3.49	7.86
57	**8h**	1.33	2.29	5.14	**40**	**8h**	1.59	2.72	6.12
55	**9h**	1.47	2.51	5.66	**38**	**9h**	1.61	2.75	6.2
53	**10h**	1.61	2.76	6.22	**32**	**10h**	1.75	3.01	6.76

XIII b: Computed wear times Actigraph Total PA (mins).

Dialysis Day Total PA mins					Non-Dialysis Day Total PA mins				
n =	Wear hours	Days required for desired reliability			n =	Wear hours	Days required for desired reliability		
		0.7	0.8	0.9			0.7	0.8	0.9
63	**4h**	0.75	1.29	2.91	**54**	**4h**	0.79	1.36	3.06
63	**5h**	0.75	1.29	2.91	**52**	**5h**	0.71	1.22	2.75
62	**6h**	0.67	1.15	2.60	**52**	**6h**	0.71	1.22	2.75
60	**7h**	0.66	1.12	2.53	**51**	**7h**	0.70	1.19	2.69
57	**8h**	0.64	1.09	2.45	**40**	**8h**	0.83	1.43	3.21
55	**9h**	0.64	1.10	2.47	**38**	**9h**	0.86	1.48	3.33
53	**10h**	0.65	1.11	2.50	**32**	**10h**	1.00	1.71	3.84

XIII c: Computed wear times Actigraph MVPA (mins).

Dialysis Day MVPA mins					Non-Dialysis Day MVPA mins				
n =	Wear hours	Days required to achieve reliability			n =	Wear hours	Days required to achieve reliability		
		0.7	0.8	0.9			0.7	0.8	0.9
63	**4h**	0.60	1.04	2.33	**54**	**4h**	0.54	0.93	2.09
63	**5h**	0.60	1.04	2.33	**52**	**5h**	0.54	0.93	2.08
62	**6h**	0.57	0.97	2.19	**52**	**6h**	0.54	0.93	2.08
60	**7h**	0.58	1.00	2.25	**51**	**7h**	0.51	0.87	1.97
57	**8h**	0.60	1.02	2.30	**40**	**8h**	0.53	0.90	2.03
55	**9h**	0.61	1.05	2.35	**38**	**9h**	0.58	0.99	2.23
53	**10h**	0.62	1.06	2.38	**32**	**10h**	0.57	0.97	2.18

Appendix XIV Computed wear times Actigraph

XIV a: Computed wear times Actigraph MVPA (% of wear time).

Dialysis Day MVPA %					Non-Dialysis Day MVPA %				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
63	**4h**	0.67	1.15	2.59	**54**	**4h**	0.53	0.91	2.05
63	**5h**	0.67	1.15	2.59	**52**	**5h**	0.54	0.93	2.09
62	**6h**	0.66	1.12	2.53	**52**	**6h**	0.54	0.93	2.09
60	**7h**	0.67	1.16	2.60	**51**	**7h**	0.51	0.87	1.95
57	**8h**	0.66	1.12	2.53	**40**	**8h**	0.52	0.89	2.00
55	**9h**	0.66	1.14	2.56	**38**	**9h**	0.55	0.95	2.13
53	**10h**	0.66	1.14	2.56	**32**	**10h**	0.56	0.97	2.18

XIV b: Computed wear times Actigraph Triaxial counts/day.

Dialysis Day Triaxial counts/day					Non-Dialysis Day Triaxial counts/day				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
63	**4h**	0.59	1.01	2.26	**54**	**4h**	0.60	1.02	2.30
63	**5h**	0.59	1.01	2.26	**52**	**5h**	0.54	0.93	2.10
62	**6h**	0.55	0.94	2.11	**52**	**6h**	0.54	0.93	2.10
60	**7h**	0.53	0.91	2.05	**51**	**7h**	0.54	0.93	2.10
57	**8h**	0.52	0.89	2.00	**40**	**8h**	0.68	1.17	2.63
55	**9h**	0.51	0.88	1.98	**38**	**9h**	0.71	1.22	2.74
53	**10h**	0.52	0.89	2.00	**32**	**10h**	0.73	1.26	2.83

XIV c: Computed wear times Actigraph Steps/day.

Dialysis Day Steps/day					Non-Dialysis Day Steps/day				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
63	**4h**	0.38	0.65	1.45	**54**	**4h**	0.90	1.54	3.47
63	**5h**	0.38	0.65	1.45	**52**	**5h**	0.38	0.65	1.45
62	**6h**	0.34	0.59	1.32	**52**	**6h**	0.38	0.65	1.45
60	**7h**	0.34	0.58	1.31	**51**	**7h**	0.34	0.59	1.32
57	**8h**	0.35	0.61	1.36	**40**	**8h**	0.34	0.58	1.31
55	**9h**	0.35	0.61	1.37	**38**	**9h**	0.35	0.61	1.36
53	**10h**	0.36	0.61	1.38	**32**	**10h**	0.35	0.61	1.37

Appendix XV Computed wear times ActivPAL.

XV a: Computed wear times ActivPAL Sit/Lie (minutes).

Dialysis Day Sit/Lie (mins)					Non-Dialysis Day Sit/Lie (mins)				
N=	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	N=	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
55	4h	2.75	4.72	10.61	47	4h	1.72	2.95	6.64
55	5h	2.75	4.72	10.61	45	5h	1.98	3.40	7.66
52	6h	1.80	3.08	6.93	43	6h	1.82	3.12	7.03
51	7h	1.62	2.77	6.23	43	7h	1.82	3.12	7.03
51	8h	1.62	2.77	6.23	37	8h	2.38	4.07	9.16
49	9h	1.59	2.72	6.11	34	9h	2.21	3.79	8.52
44	10h	1.05	1.80	4.05	24	10h	2.81	4.82	10.84

XV b: Computed wear times ActivPAL Stand time (minutes).

Dialysis Day Stand time (mins)					Non-Dialysis Day Stand time (mins)				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
55	4h	1.09	1.87	4.21	47	4h	1.16	2.00	4.49
55	5h	1.09	1.87	4.21	45	5h	1.02	1.74	3.92
52	6h	1.04	1.78	4.01	43	6h	1.22	2.08	4.69
51	7h	1.00	1.71	3.86	43	7h	1.22	2.08	4.69
51	8h	1.00	1.71	3.86	37	8h	1.26	2.16	4.86
49	9h	1.19	2.04	4.59	34	9h	1.65	2.84	6.38
44	10h	1.09	1.86	4.19	24	10h	1.04	1.78	4.01

XV c: Computed wear times ActivPAL Stepping time (minutes).

Dialysis Day Stepping time (mins)					Non-Dialysis Day Stepping time (mins)				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
55	4h	0.81	1.38	3.11	47	4h	0.90	1.54	3.47
55	5h	0.81	1.38	3.11	45	5h	0.82	1.41	3.17
52	6h	0.65	1.11	2.49	43	6h	0.85	1.45	3.27
51	7h	0.60	1.03	2.32	43	7h	0.85	1.45	3.27
51	8h	0.60	1.03	2.32	37	8h	0.91	1.57	3.53
49	9h	0.70	1.19	2.69	34	9h	1.03	1.77	3.97
44	10h	0.66	1.12	2.53	24	10h	0.88	1.50	3.38

Appendix XVI Computed wear times ActivPAL.

XVI a: Computed wear times ActivPAL Stepping time (% of wear time).

Dialysis Day Stepping time (%)					Non-Dialysis Day Stepping time (%)				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
55	4h	0.71	1.22	2.75	47	4h	0.73	1.25	2.80
55	5h	0.71	1.22	2.75	45	5h	0.75	1.28	2.89
52	6h	0.68	1.17	2.63	43	6h	0.78	1.34	3.02
51	7h	0.65	1.12	2.52	43	7h	0.78	1.34	3.02
51	8h	0.65	1.12	2.52	37	8h	0.88	1.51	3.39
49	9h	0.73	1.26	2.83	34	9h	0.90	1.54	3.47
44	10h	0.70	1.20	2.71	24	10h	0.90	1.54	3.47

XVI b: Computed wear times ActivPAL Steps/day.

Dialysis Day Steps/day					Non-Dialysis Day Steps/day				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
55	4h	0.82	1.40	3.14	47	4h	0.78	1.34	3.01
55	5h	0.82	1.40	3.14	45	5h	0.71	1.22	2.75
52	6h	0.63	1.08	2.42	43	6h	0.74	1.26	2.84
51	7h	0.59	1.02	2.29	43	7h	0.74	1.26	2.84
51	8h	0.59	1.02	2.29	37	8h	0.81	1.39	3.13
49	9h	0.69	1.17	2.64	34	9h	0.93	1.59	3.57
44	10h	0.66	1.13	2.54	24	10h	0.85	1.46	3.28

XVI c: Computed wear times ActivPAL Transitions/day.

Dialysis Day Transitions/day					Non-Dialysis Day Transitions/day				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
55	4h	2.09	3.59	8.08	47	4h	2.00	3.44	7.73
55	5h	2.09	3.59	8.08	45	5h	1.85	3.17	7.14
52	6h	1.67	2.87	6.45	43	6h	1.97	3.38	7.60
51	7h	1.80	3.09	6.95	43	7h	1.97	3.38	7.60
51	8h	1.80	3.09	6.95	37	8h	1.99	3.41	7.67
49	9h	2.03	3.48	7.82	34	9h	2.94	5.05	11.36
44	10h	1.55	2.67	6.00	24	10h	3.41	5.85	13.17

Appendix XVII Computed wear times ActivPAL.

XVII a: Computed wear times ActivPAL Transitions/hour.

Dialysis Day Transitions/hour					Non-Dialysis Day Transitions/hour				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
55	**4h**	1.87	3.21	7.23	**47**	**4h**	1.25	2.14	4.81
55	**5h**	1.87	3.21	7.23	**45**	**5h**	1.15	1.98	4.45
52	**6h**	1.61	2.76	6.20	**43**	**6h**	1.20	2.06	4.63
51	**7h**	1.69	2.90	6.52	**43**	**7h**	1.20	2.06	4.63
51	**8h**	1.69	2.90	6.52	**37**	**8h**	1.18	2.03	4.57
49	**9h**	1.77	3.03	6.82	**34**	**9h**	1.44	2.46	5.54
44	**10h**	1.68	2.88	6.49	**24**	**10h**	1.83	3.14	7.06

XVII b: Computed wear times ActivPAL Energy Expenditure per day.

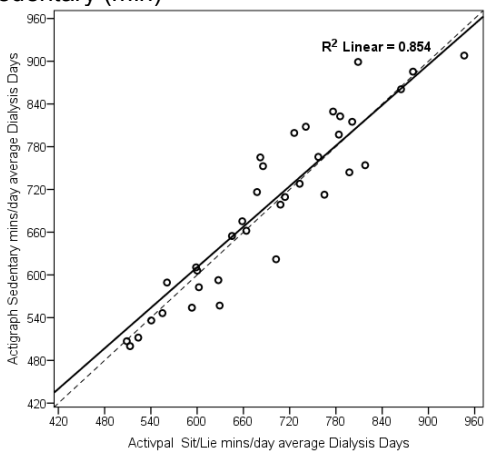
Dialysis Day EE/day					Non-Dialysis Day EE/day				
n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9	n =	Wear hours	Days required to achieve reliability 0.7	0.8	0.9
55	**4h**	2.00	3.42	7.70	**47**	**4h**	4.02	6.89	15.50
55	**5h**	2.00	3.42	7.70	**45**	**5h**	2.42	4.14	9.32
52	**6h**	1.07	1.84	4.14	**43**	**6h**	2.15	3.69	8.31
51	**7h**	0.95	1.62	3.65	**43**	**7h**	2.15	3.69	8.31
51	**8h**	0.95	1.62	3.65	**37**	**8h**	2.24	3.85	8.66
49	**9h**	1.04	1.78	4.00	**34**	**9h**	3.17	5.44	12.24
44	**10h**	0.63	1.08	2.43	**24**	**10h**	1.96	3.36	7.55

Appendix XVIII: Results of normality testing of sedentary and PA outcomes.

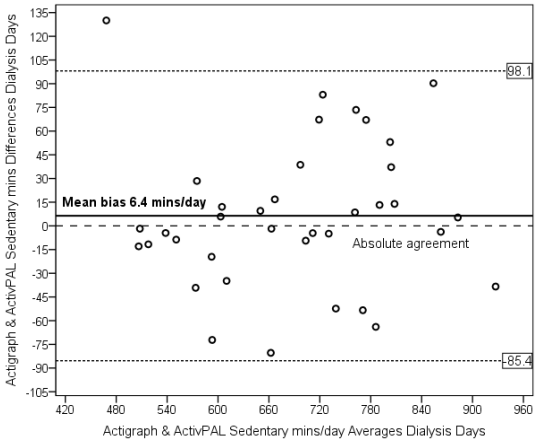
Outcome	ActivPAL			Actigraph			Seven Day recall		
	Statistic	df	Sig.	Statistic	df	Sig.	Statistic	df	Sig.
Sedentary (min)	0.977	37	0.636	0.985	37	0.885			
Sedentary (%)	0.915	37	0.008	0.898	37	0.003			
Light PA (min)				0.969	39	0.361	0.942	69	0.003
Moderate PA (min)				0.858	39	0	0.753	39	0
Vigorous PA (min)				0.227	39	0	0.609	39	0
MVPA (min)				0.869	39	0	0.755	39	0
Total PA (min)	0.939	37	0.042	0.917	37	0.009			
Total PA (%)	0.915	37	0.008	0.898	37	0.003			
Steps / day	0.771	37	0	0.764	37	0			
Steps / minute	0.774	37	0	0.765	37	0			
Counts/day	0.787	37	0	0.757	37	0			
Counts/min	0.786	37	0	0.769	37	0			
EE (kcals)				0.631	39	0	0.845	39	0
EE (MET mins)	0.969	35	0.411				0.935	35	0.039
EE (MET mins)	0.980	37	0.736	0.962	37	0.237			

Appendix XIX – Concordance ActivPAL/Actigraph

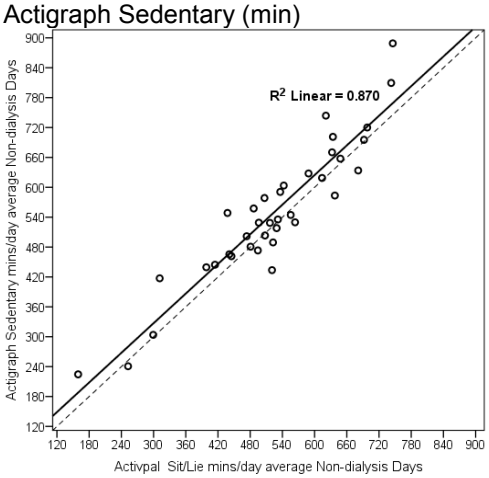
XIX a: Dialysis day - ActivPAL v Actigraph Sedentary (min)



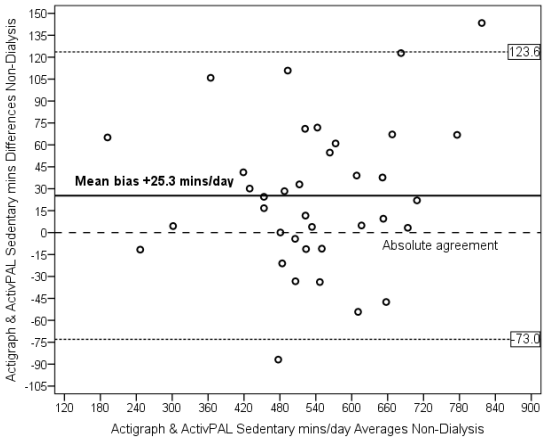
XIX b: Dialysis day - ActivPAL & Actigraph Sedentary (min) LOA



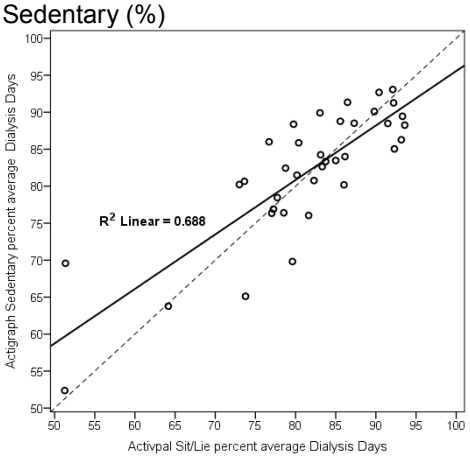
XIX c: Non-dialysis day - ActivPAL v Actigraph Sedentary (min)



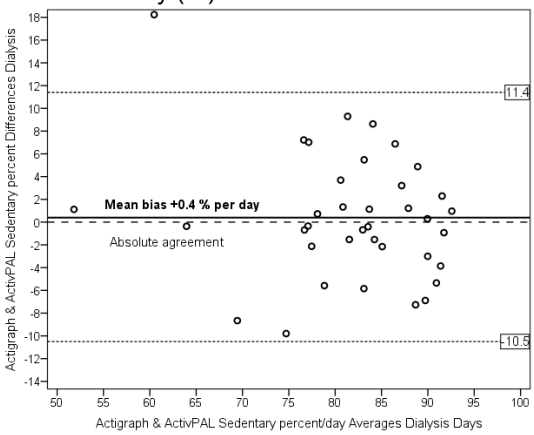
XIX d: Dialysis day - ActivPAL & Actigraph Sedentary (min) LOA



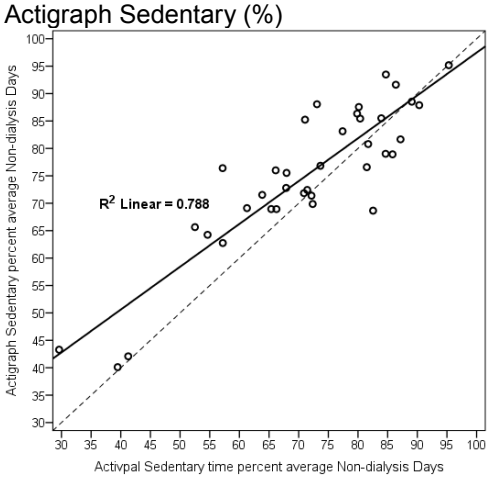
XIX e: Dialysis day - ActivPAL v Actigraph Sedentary (%)



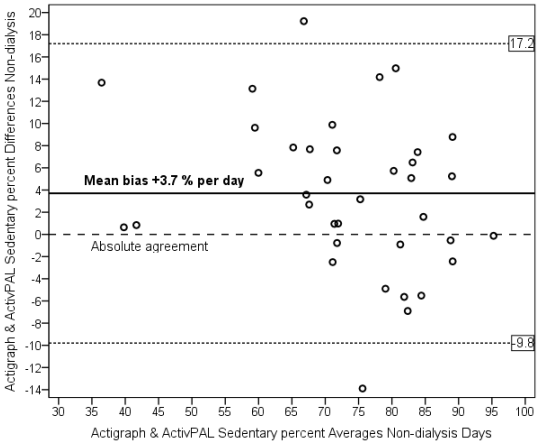
XIX f: Dialysis day - ActivPAL & Actigraph Sedentary (%) LOA



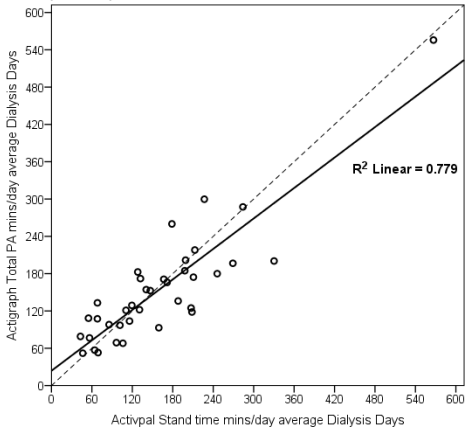
XIX g: Non-dialysis day ActivPAL v Actigraph Sedentary (%)



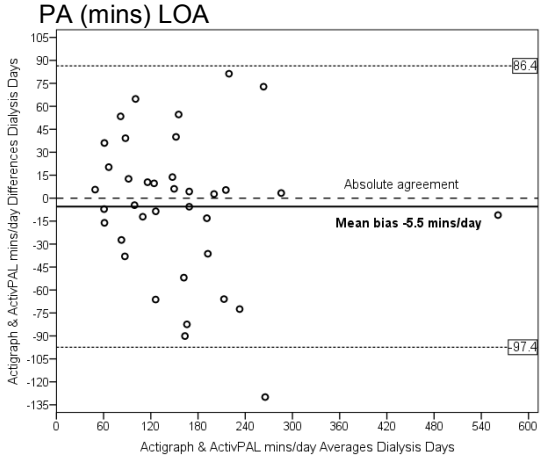
XIX h: Non-dialysis day ActivPAL & Actigraph Sedentary (%) LOA



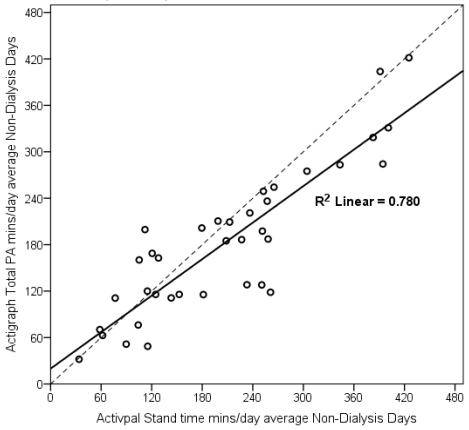
XIX i: Dialysis day Actigraph v ActivPAL total PA (mins)



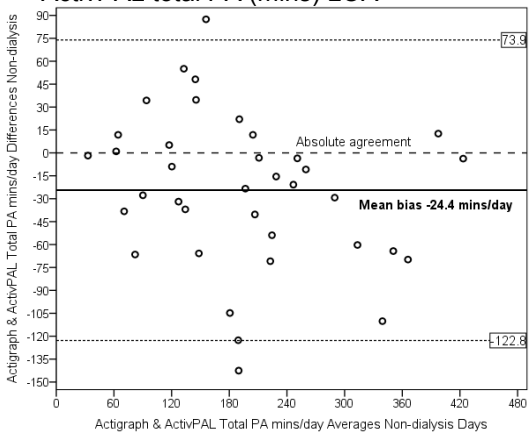
XIX j: Dialysis day Actigraph v ActivPAL total PA (mins) LOA



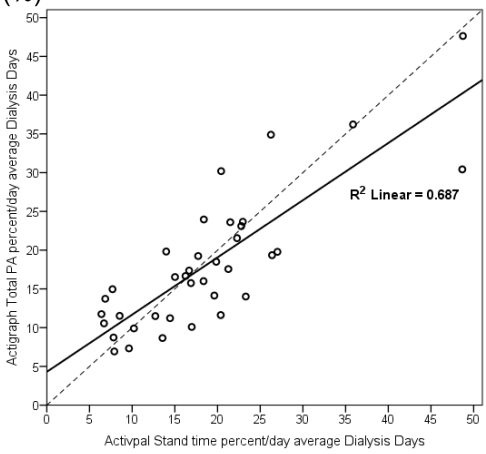
XIX k: Non-dialysis day Actigraph v ActivPAL total PA (mins)



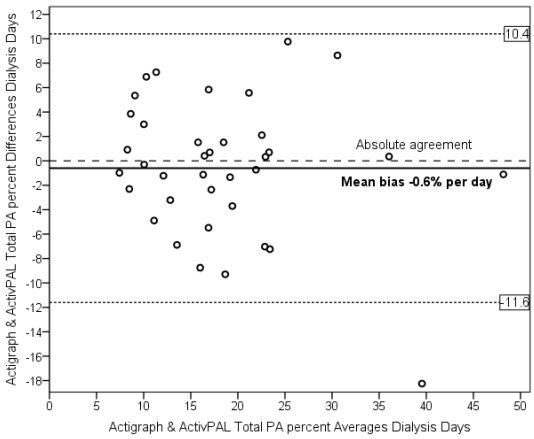
XIX l: Non-dialysis day Actigraph v ActivPAL total PA (mins) LOA



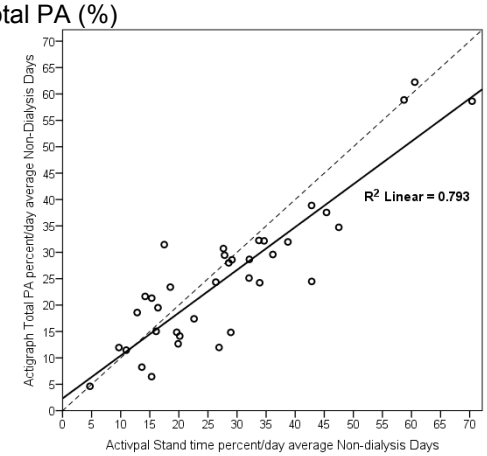
XIX m: Dialysis day Actigraph v ActivPAL total PA (%)



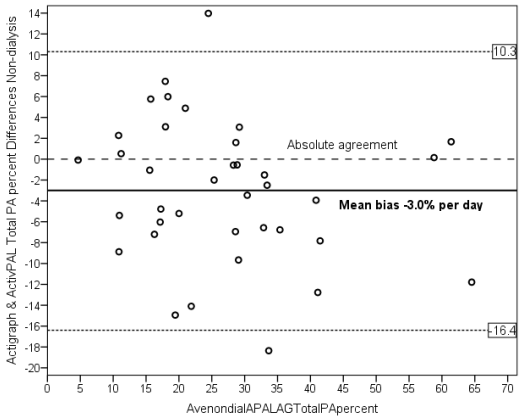
XIX n: Dialysis day Actigraph & ActivPAL total PA (%) LOA



XIX o: Non-dialysis day Actigraph v ActivPAL total PA (%)

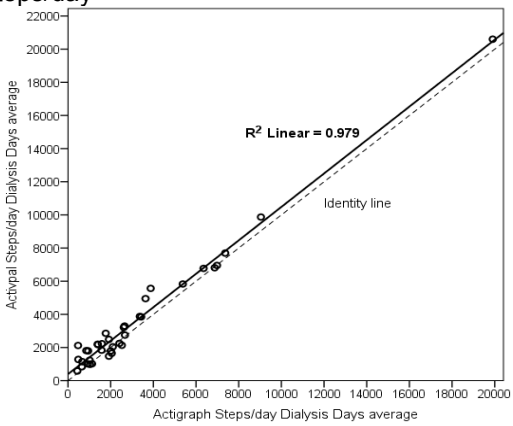


XIX p: Non-dialysis day Actigraph & ActivPAL total PA (%) LOA

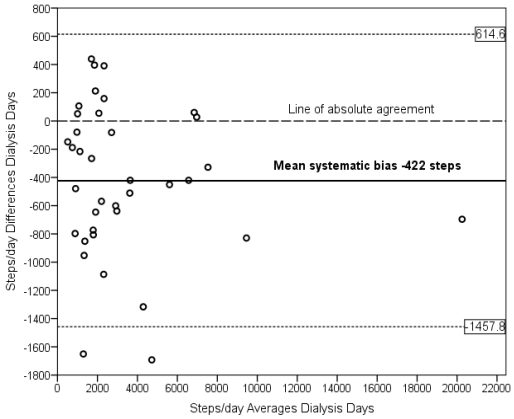


Appendix XX - Concordance ActivPAL/Actigraph

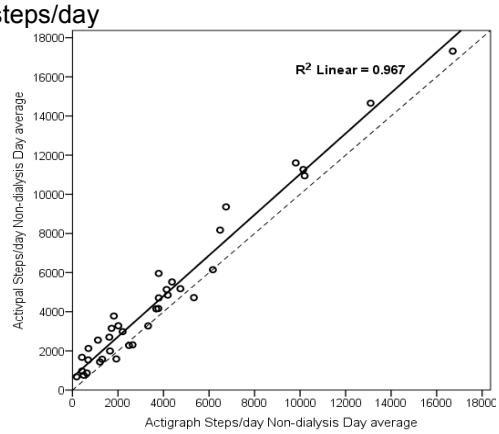
XX a: Dialysis day Actigraph v ActivPAL steps/day



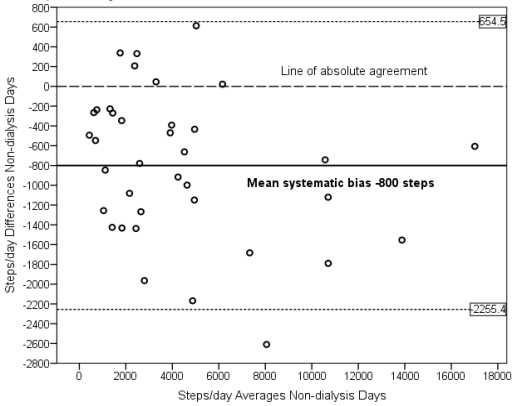
XX b: Dialysis day Actigraph v ActivPAL steps/day



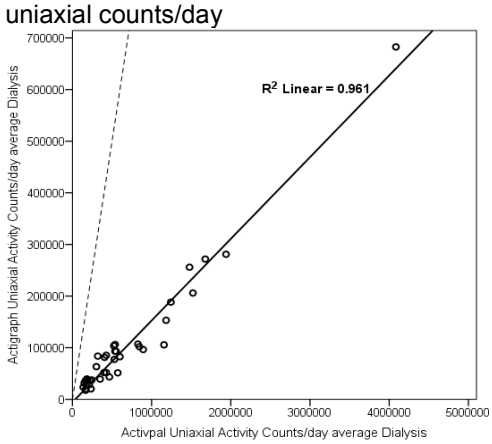
XX c: Non-dialysis day Actigraph v ActivPAL steps/day



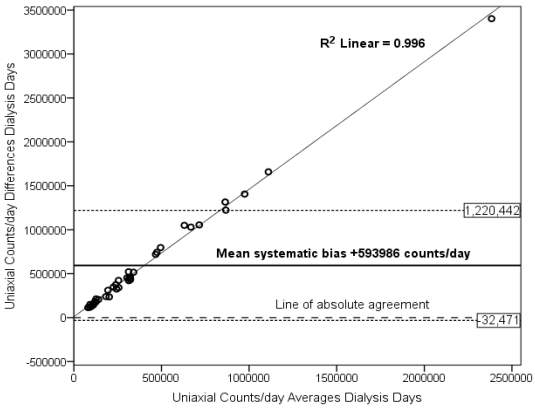
XX d: Non-dialysis day Actigraph & ActivPAL steps/day



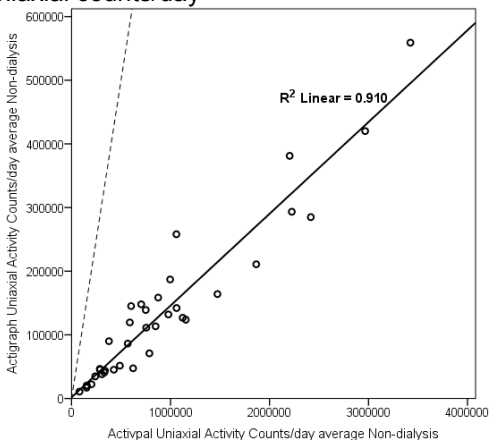
XX e: Dialysis day Actigraph v ActivPAL uniaxial counts/day



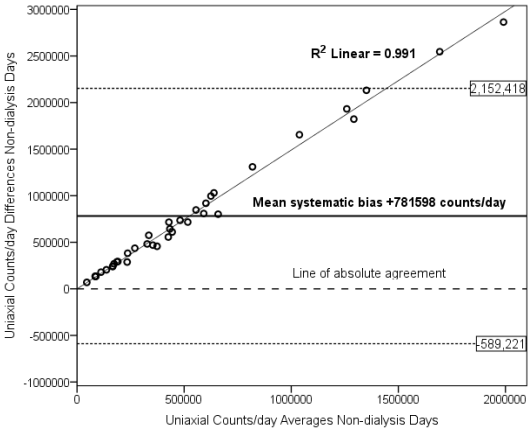
XX f: Dialysis day Actigraph &ActivPAL uniaxial counts/day LOA



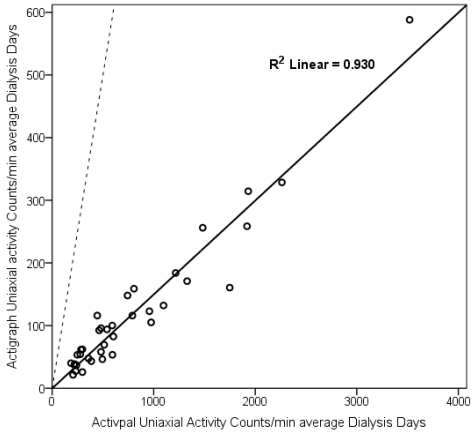
XX g: Non-Dialysis day Actigraph v ActivPAL uniaxial counts/day



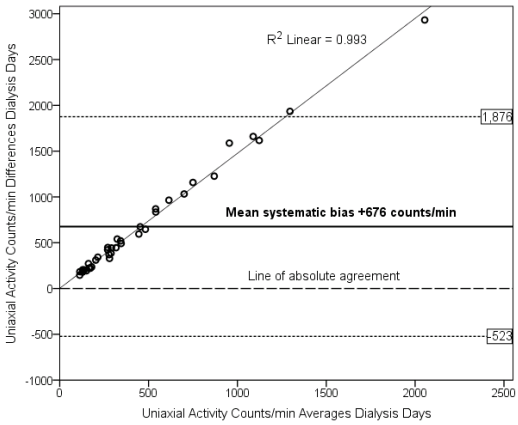
XX h: Non-Dialysis day Actigraph v ActivPAL uniaxial counts/day



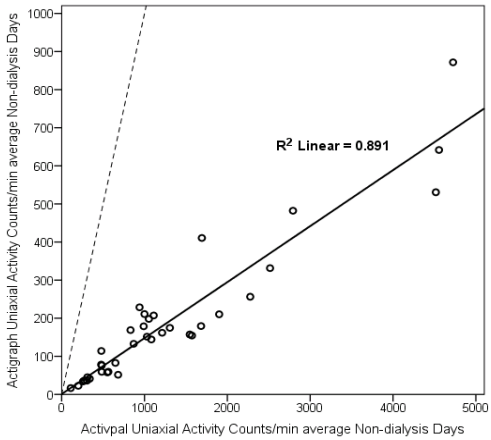
XX i: Dialysis day Actigraph v ActivPAL uniaxial counts/min



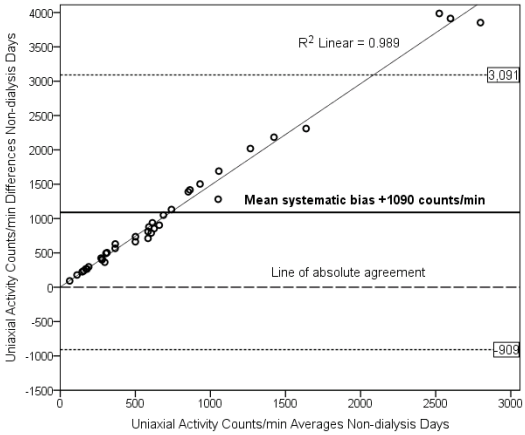
XX j: Dialysis day Actigraph & ActivPAL uniaxial counts/min LOA



XX k: Non-Dialysis day Actigraph v ActivPAL uniaxial counts/min

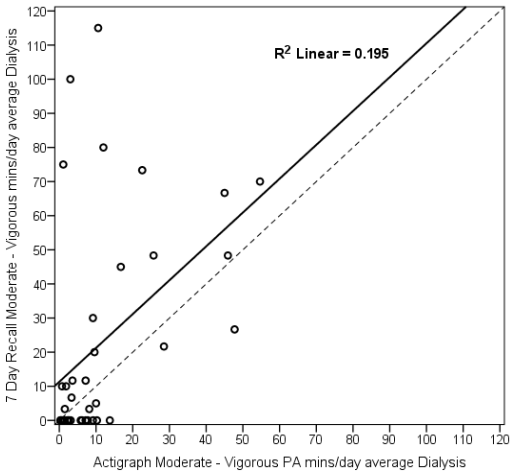


XX l: Non-Dialysis day Actigraph v ActivPAL uniaxial counts/min

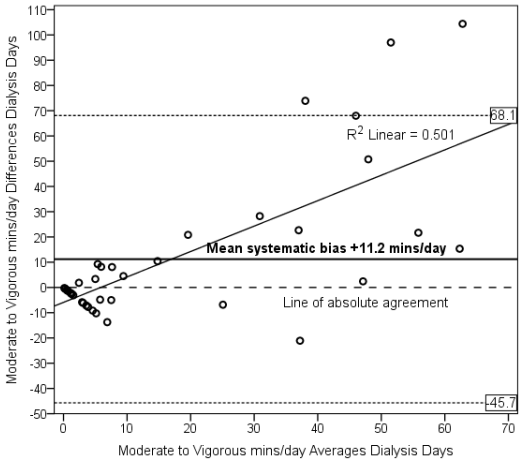


Appendix XXI Concordance 7DR/Actigraph

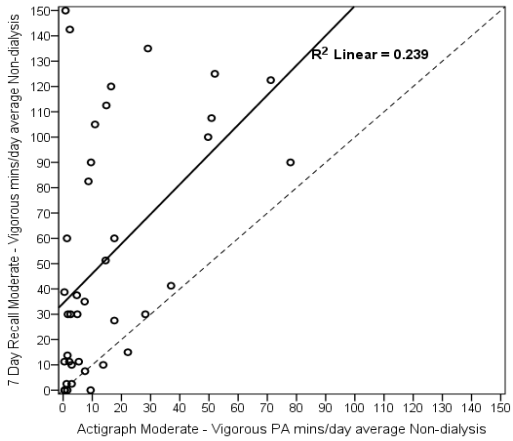
XXI a: Dialysis day 7DR v Actigraph MVPA (min)



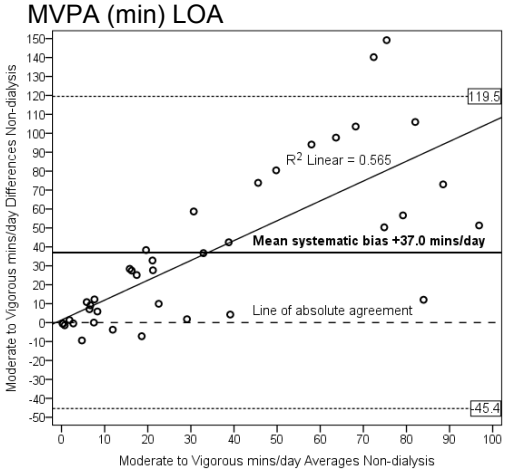
XXI b: Dialysis day 7DR & Actigraph MVPA (min) LOA



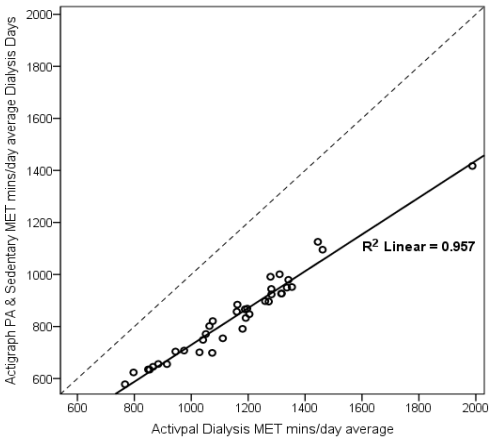
XXI c: Non-dialysis day 7DR v Actigraph MVPA (min)



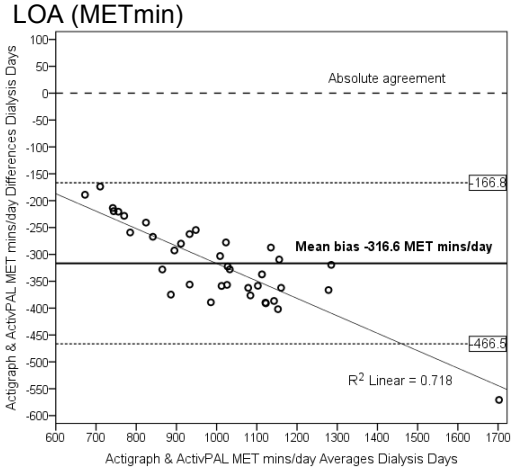
XXI d: Non-dialysis day 7DR & Actigraph MVPA (min) LOA



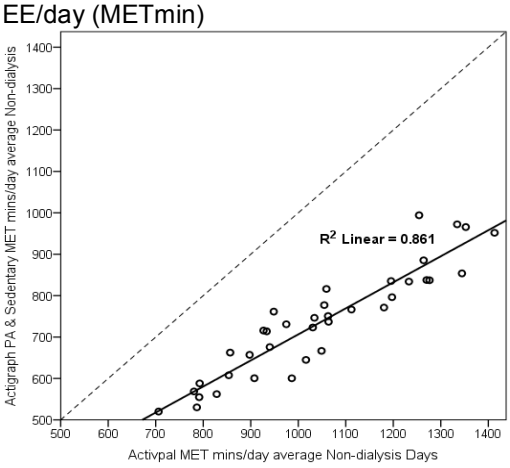
XXI e: Dialysis day 7DR v Actigraph EE/day (METmin)



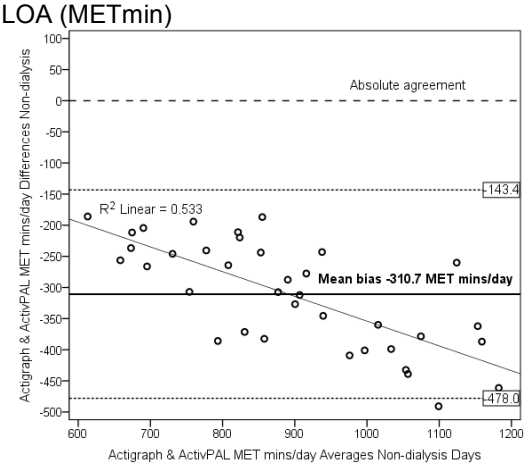
XXI f: Dialysis day 7DR & Actigraph EE/day LOA (METmin)



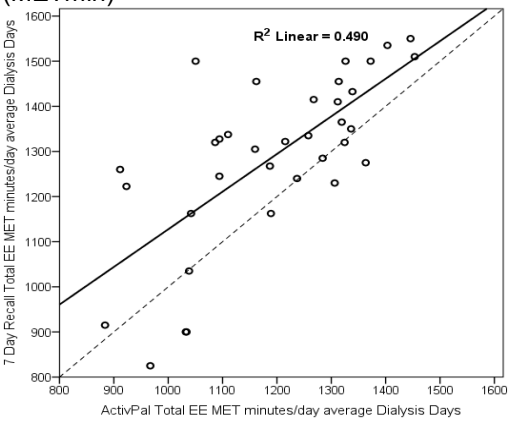
XXI g: Non-dialysis day 7DR v Actigraph EE/day (METmin)



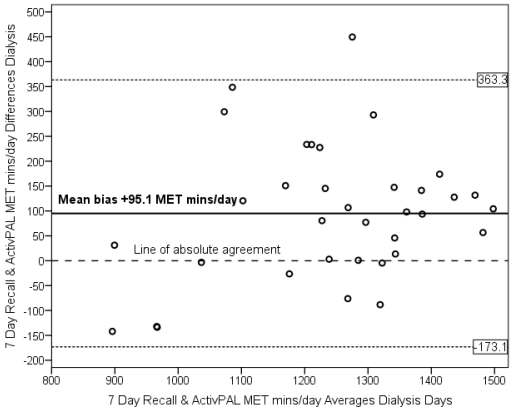
XXI h: Non-dialysis day 7DR & Actigraph EE/day LOA (METmin)



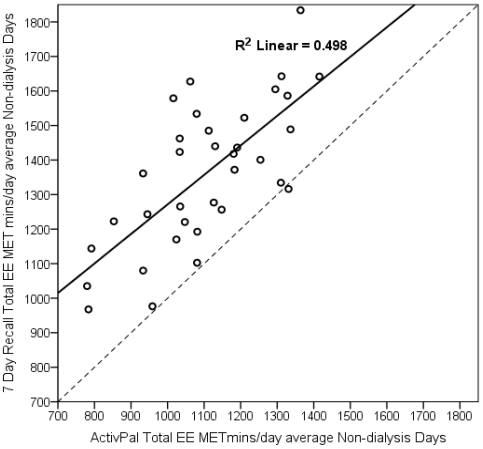
XXI i: Dialysis day 7DR v ActivPAL EE/day (METmin)



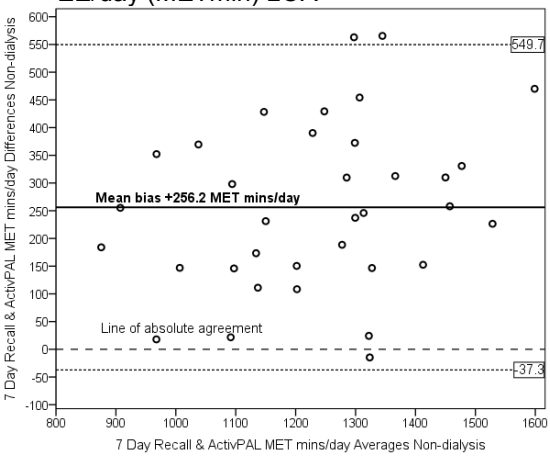
XXI j: Dialysis day 7DR & ActivPAL EE/day (METmin) LOA



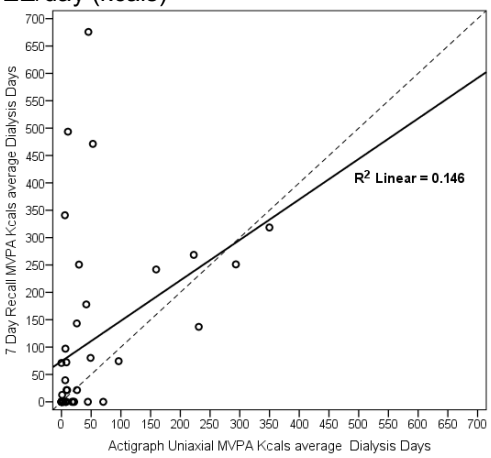
XXI k: Non-dialysis day 7DR v ActivPAL EE/day (METmin)



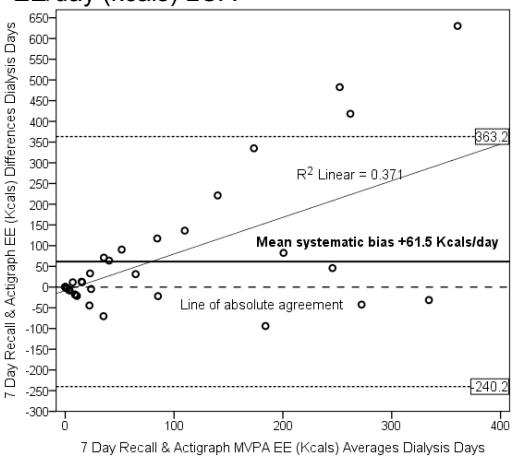
XXI l: Non-dialysis day 7DR & ActivPAL EE/day (METmin) LOA



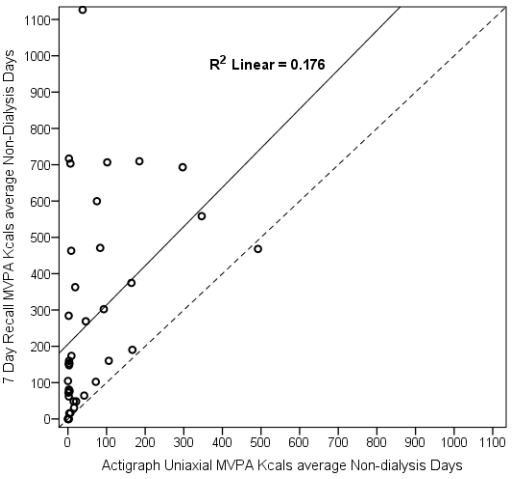
XXI m: Dialysis day 7DR v Actigraph MVPA EE/day (kcals)



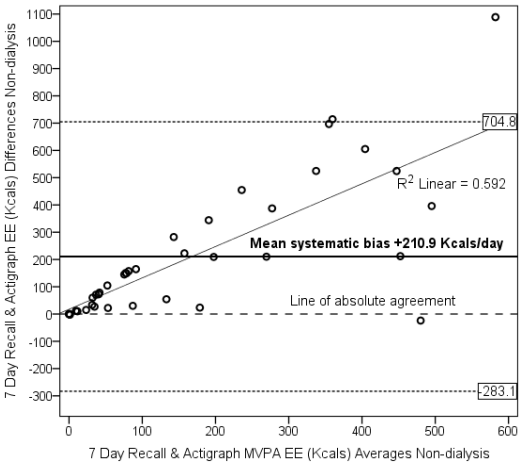
XXI n: Dialysis day 7DR & Actigraph MVPA EE/day (kcals) LOA



XXI o: Non-dialysis day 7DR v Actigraph MVPA EE/day (kcals)



XXI p: Non-dialysis day 7DR & Actigraph MVPA EE/day (kcals) LOA



Appendix XXII Participant characteristics chapter 5

Appendix XXII a: Participant characteristics.

Participant Characteristic	Total sample	Sample with sufficient PA data
Age *(years)*	55.6 ± 15.6	57.5 ± 15.5
Gender *M/F (%)*	48/25 (66/34)	40 / 23 (63/37)
Body Mass Index *(kg/m^2)*	28.5 ± 6.3	28.7 ± 6.3
Resting Heart rate *(bpm)*	72.0 ± 13.0	71.7 ± 12.4
Systolic *(mmHg)*	135.6 ± 24.5	134.7 ± 23.8
Diastolic *(mmHg)*	77.6 ± 12.0	75.5 ± 9.8
Systemic pulse pressure *(mmHg)*	52 (43 - 70)	53 (43 - 70)
Mean arterial pressure *(mmHg)*	96.9 ± 13.8	95.2 ± 11.9
Haemodialysis Vintage *(months)*	16.8 (6.7 - 32.7)	14.8 (6.8 - 31.4)
Renal Replacement Therapy Vintage *(months)*	25.9 (8.1 - 68.8)	25.9 (8.3 - 69.3)
Haemoglobin *(g/dL)*	11.2 ± 1.0	11.2 ± 1.0
Haematocrit *(%)*	33.9 ± 3.2	33.9 ± 3.2
C-reactive protein *(mg/L)*	0 (0 - 10.0)	0 (0 – 10.0)
Dialysis Adequacy *(%)*	71 (66 - 75)	71 (66 - 75)
Albumin *(g/L)*	39.0 (36.0 - 42.0)	39.0 (36.0 - 41.0)
Troponin T *(ng/L)*	37 (20.5 - 69.5)	37.0 (21.0 - 69.0)
Corrected Calcium serum level *(mmol/L)*	2.36 ± 0.17	2.37 ± 0.17
Phosphate *(mmol/L)*	1.43 ± 0.41	1.40 ± 0.33
Parathyroid level *(mmol/L)*	16.8 (9.9 - 30.6)	16.4 (9.7 - 30.9)
Creatinine pre-dialysis *(mmol/L)*	683 (558 - 672)	644 (546 - 856)
Total number of medications	9 (7 - 12)	10 (8 - 12)
Number of comorbidities, *(N)*	1.0 ± 0.8	1.0 ± 0.8
• Hypertension *(%)*	42 (58)	35 (56)
• Diabetes mellitus *(%)*	16 (22)	16 (24)
• Cardiovascular disease *(%)*	14 (19)	13 (21)

Appendix XXII b: Determination of physical performance, functional status outcome, and physical activity differences between male and female participants.

Outcome	n =	Recruited sample	n =	Sample with PA data
Hand grip strength	72	t(70)=7.43, p <0.001, d =0.88	63	t(61) = 6.62, p <0.001, d = 0.83
Sit-to-stand 5	70	Z = -0.65, p =0.52,	61	Z = -0.40, P = 0.69
Timed up-and-go	72	Z = 0, p = 1.0	63	Z = -0.36, p = 0.72
ISWT	69	Z = -0.10, p = 0.92	61	Z = -0.28, p = 0.78
Duke	73	Z = -2.62, p = 0.01, r = 0.31	63	Z = -2.321, p = 0.02, r = 0.29
KDQOL-SF PCS	65	Z = -2.20, p = 0.03, r = 0.27	58	Z = -2.129, p = 0.03, r = 0.28
Physical activity			63	Z = -2.027, p = 0.04, r = 0.26

Appendix XXIII Shuttle Walk Test outcomes

Appendix XXIII a: Results of multiple regression analyses for Incremental Shuttle Walk Test outcome variables.

Variable	Shuttle walk test distance (m)	Shuttle walk test gait speed (m/s)	Shuttle walk test fitness (METs)
	Unstandardized β Coefficient (Lower, Upper bound)	Unstandardized β Coefficient (Lower, Upper bound)	Unstandardized β Coefficient (Lower, Upper bound)
Age	-5.98*** (-8.85, -3.1)	-0.01*** (-0.02, -0.01)	-0.04** (-0.07, -0.02)
BMI	-8.62* (-15.54, -1.70)	-0.02** (-0.032, -0.004)	-0.07* (-0.14, -0.01)
Medications	-17.29* (-31.14, -3.44)	-0.04** (-0.07, -0.01)	-0.19** (-0.32, -0.05)
r	0.63	0.64	0.59
r^2	0.40	0.41	0.35
r^2 adjusted	0.37	0.38	0.32

Appendix XXIII b: Results of Incremental Shuttle Walk Test multiple regression analyses with physical activity as additional predictor variable.

Variable	Shuttle walk test distance (m)	Shuttle walk test gait speed (m/s)	Shuttle walk test fitness (METs)
	Unstandardized β Coefficient (Lower, Upper bound)	Unstandardized β Coefficient (Lower, Upper bound)	Unstandardized β Coefficient (Lower, Upper bound)
Age	-3.568** (-6.09, -1.04)	-0.008** (-0.014, -0.002)	-0.029* (-0.056, -0.002)
BMI	-6.91* (-12.59, -1.23)	-0.015** (-0.028, -0.002)	-0.063* (-0.123, -0.002)
Medications	-11.51* (-22.58, -0.44)	-0.026** (-0.051, -0.002)	-0.145* (-0.263, -0.027)
PA	0.47 *** (0.31, 0.64)	0.001*** (0.001, 0.001)	0.003** (0.001, 0.005)
r	0.79	0.76	0.69
r^2	0.62	0.57	0.48
r^2 adjusted	0.59	0.54	0.44

Appendix XXIV Participant characteristics chapter 6

Participant characteristics whole sample and participants with sufficient PA data for final analyses.

Characteristic	Total sample n = 73	Sample with sufficient PA data n = 63
Age *(years)*	55.6 ± 15.6	57.5 ± 15.5
Gender *M/F (%)*	48/25 (66/34)	40 / 23 (63/37)
Weight	81.0 ±17.5	80.5 ± 16.4
Height	167.7 ± 16.6	166.5 ± 17.2
Body Mass Index *(kg/m^2)*	28.5 ± 6.3	28.7 ± 6.3
Resting Heart rate *(bpm)*	72.0 ± 13.0	71.7 ± 12.4
Systolic *(mmHg)*	135.6 ± 24.5	134.7 ± 23.8
Diastolic *(mmHg)*	77.6 ± 12.0	75.5 ± 9.8
Systemic pulse pressure *(mmHg)*	52 (43 - 70)	53 (43 - 70)
Mean arterial pressure *(mmHg)*	96.9 ±13.8	95.2 ± 11.9
Haemodialysis Vintage *(months)*	16.8 (6.7 - 32.7)	14.8 (6.8 - 31.4)
Renal Replacement Therapy Vintage *(months)*	25.9 (8.1 - 68.8)	25.9 (8.3 - 69.3)
Haemoglobin *(g/dL)*	11.2 ± 1.0	11.2 ± 1.0
Haematocrit *(%)*	33.9 ± 3.2	33.9 ± 3.2
C-reactive protein *(mg/L)*	0 (0 - 10.0)	0 (0 - 10.0)
Dialysis Adequacy *(%)*	71 (66 - 75)	71 (66 - 75)
Albumin *(g/L)*	39.0 (36.0 - 42.0)	39.0 (36.0 - 41.0)
Troponin T *(ng/L)*	37 (20.5 - 69.5)	37.0 (21.0 - 69.0)
Corrected Calcium serum level *(mmol/L)*	2.36 ± 0.17	2.37 ± 0.17
Phosphate *(mmol/L)*	1.43 ± 0.41	1.40 ± 0.33
Parathyroid level *(mmol/L)*	16.8 (9.9 - 30.6)	16.4 (9.7 - 30.9)
Creatinine pre-dialysis *(mmol/L)*	683 (558 - 672)	644 (546 - 856)
Number of vasoactive medications	2 (1 - 3.5)	2 (1 - 3)
Number of comorbidities, *(N)*	1.0 ± 0.8	1.0 ± 0.8
• Hypertension *(%)*	42 (58)	35 (56)
• Diabetes mellitus *(%)*	16 (22)	16 (24)
• Cardiovascular disease *(%)*	14 (19)	13 (21)
Shuttle walk test distance	280 (170 - 440)[¥]	280 (150 - 430)[¥¥]
Pulse wave velocity	7.50 (6.3 - 9.0)	7.6 (6.4 - 9.4)
	8.03 ± 2.3[†]	8.10 ± 2.3[†]
Augmentation Index	20.4 ± 7.5	20.9 ± 6.9

[†]data non-normally distributed, mean ± std dev presented for comparison
[¥]n = 69, [¥¥]n = 61

Appendix XXV PWV univariable associations

Appendix XXV a: Univariable associations with pulse wave velocity participants with sufficient PA data (n = 63).

Variable	Unstandardized β (Lower, Upper)	Pearson r
Age	0.10*** (0.07, 0.13)	0.45***
Systolic Bp	0.05*** (0.02, 0.07)	0.23***
Troponin-T	0.01** (0, 0.02)	0.11**
Serum phosphate	-2.19* (-3.89, -0.48)	-0.10**
Diabetic status	1.57* (0.26, 2.88)	0.09*
HD Vintage	0.02* (0, 0.04)	0.08*
Vasoactive Medications	0.42* (0.05, 0.78)	0.09*
Creatinine (predialysis)	-0.003* (-0.006, 0)	-0.07*
Creatinine (postdialysis)	-0.006 (-0.013, 0)	-0.06, p = 0.07
Comorbidity number	0.7 (-0.03, 1.42)	0.06, p = 0.06
Gender	-1.09 (-2.27, 0.09)	-0.05, p = 0.07
Physical Activity	-0.003*(-0.005, -0.001)	-0.09**
ISWT †	-0.005** (-0.007, -0.002)	-0.18***

†n = 61

Appendix XXV b: Univariable associations with augmentation index participants with sufficient PA data (n = 63).

Variable	Unstandardized β (Lower, Upper)	Pearson r
Heart rate	-0.18* (-0.31, -0.04)	-0.11**
Height	-0.106* (-0.205, -0.007)	-0.07*
Age	0.1 (-0.013, 0.214)	0.05, p = 0.08
BMI	0.24 (-0.035, 0.513)	0.05, p = 0.09
Haematocrit †	0.48 (-0.07, 1.03)	0.05, p = 0.08
Haemoglobin	1.16 (-0.60, 2.93)	0.03, p = 0.19
Physical activity†	-0.005 (-0.012, 0.003)	0.05, p = 0.11
ISWT ††	-0.008* (-0.017, 0)	0.07*

†n = 62 ††n = 61

Appendix XXVI PWV multivariable regression

Appendix XXVI a: Results of pulse wave velocity multivariable regression analysis with model adjusted for MAP, gender, heart rate.

Variable	Unstandardized β (Lower, Upper)
Age	0.08*** (0.054, 0.106)
Troponin T	0.01** (0.003, 0.016)
Creatinine (post-dialysis)	-0.004* (-0.008, 0.000)
HD Vintage	0.015* (0.001, 0.029)
Mean arterial pressure	0.038* (0.008, 0.068)
r	0.77
r^2	0.60
r^2 (adjusted)	0.57

*p < 0.05, ** p < 0.01, ***p < 0.001, n = 71

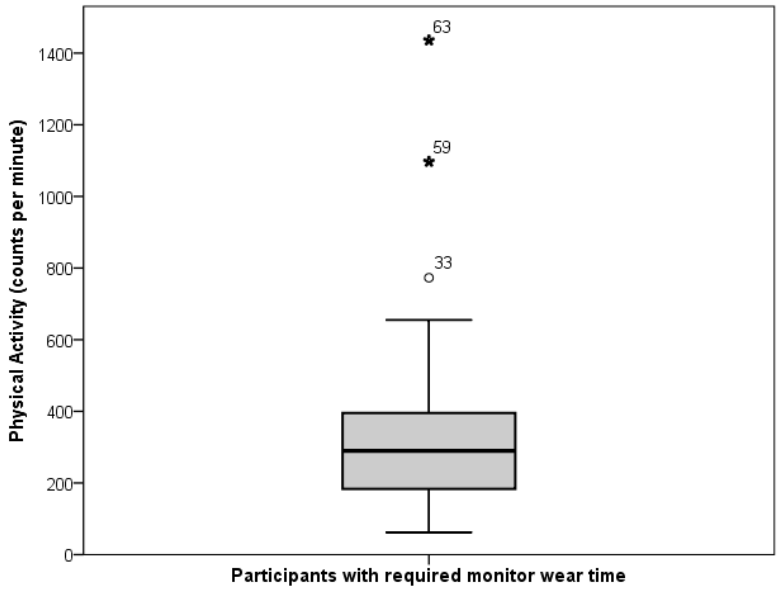
Appendix XXVI b: Results of AI multivariable regression analysis with model adjusted for MAP.

Variable	Unstandardized β (Lower, Upper)
Age	0.13** (0.04, 0.23)
Height	-0.15** (-0.24, -0.07)
Body mass index	0.313* (0.07, 0.56)
Resting heart rate	-0.19** (-0.31, -0.07)
Haemoglobin	1.69* (0.31, 3.07)
Mean arterial pressure	0.12* (0.01, 0.22)
r	0.66
r^2	0.44
r^2 (adjusted)	0.38

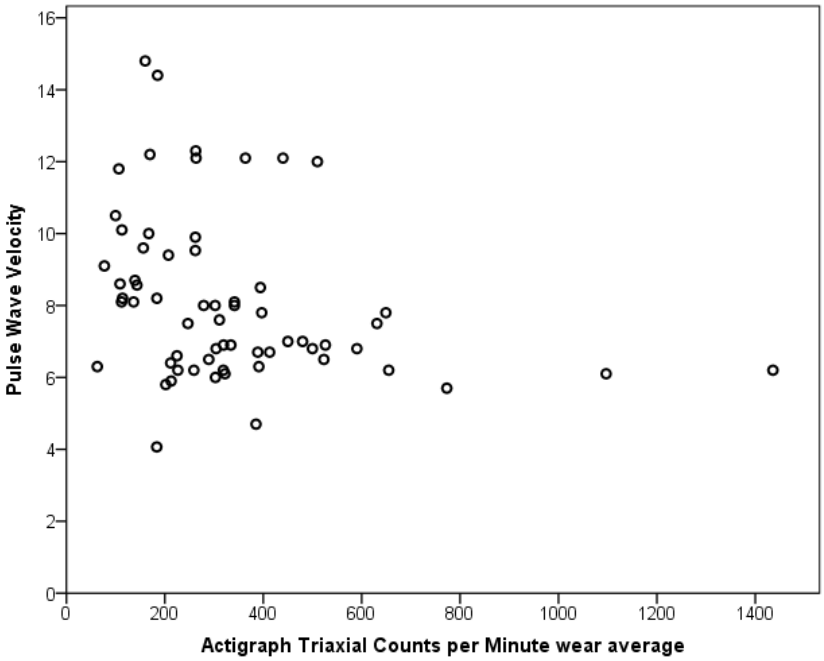
*p < 0.05, ** p < 0.01, ***p < 0.001, n = 71

Appendix XXVII Boxplot and scatterplot behavioural outliers

Appendix XXVII a: Boxplot of participant physical activity level.



Appendix XXVII b: Scatterplot of PWV versus habitual PA



Appendix XXVIII Smart technology vs research accelerometer price

Research accelerometers used in this study	Manufacturer	Price per unit and ancillaries
ActivPAL	PAL Technologies Ltd, Glasgow	£405 – 465 + £390 (software licence) + £7 for 10 'stickies'/week
Actigraph GT3X	Actigraphcorp, Pensacola, Florida	£452 (monitor +software licence)
Consumer wearables		**Price range**
Apple Watch	Apple Inc, California, USA	£479 - 949
Fitbit	Fitbit Inc, San Francisco, USA	£99 - 119
Nike Fuelband	Nike Inc, Beaverton, USA	£60 - 179
Samsung Gearfit	Samsung Group, Korea	£58 - 129
Sony Smartband SWR10	Sony Corp, Tokyo, Japan	£25 - 100
Jawbone UP3	Jawbone, San Francisco, USA	£130 - 150
Withings Activite and Pulse Ox	Issy-les-Moulineaux, France	£70

Appendix XXIX Fried Frailty criteria

Application of adapted Fried et al. (2001) frailty criteria.

Frailty is determined by an individual meeting three of the five criteria for frailty proposed by Fried et al. (2001): unintentional weight loss; weakness (grip strength); slow gait; exhaustion; low physical activity.

- The KDQOL-SF 'vitality' subscale was substituted for self-reported exhaustion from the Centre for Epidemiological Studies Depression scale (Johansen et al. 2007; Bao et al 2012; Painter and Kuskowski 2013).
- Instead of the original 15 foot average gait speed test, terminal gait speed from the incremental shuttle walk test was employed. If a participant's terminal gait speed was below 1.2 m/s, the threshold required to walk across a pedestrian crossing safely (Asher et al 2012) they were classified as having 'slow gait'.
- A body mass index below 18.5 kg/m^2 was used as a surrogate for 'shrinkage' or unintentional weight loss as previously used by Painter and Kuskowski 2013.
- Participants' Actigraph data were employed to classify individuals with 'low PA'. Accumulation of less than 50 minutes/day of all PA (defined as >100 cpm), which is predictive of mobility deterioration in stage 5 CKD (Kutsuna et al 2010) was employed.